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CARBON-13 NMR: CONFORMATION ANALYSIS OF NITROGEN  
AND PHOSPHORUS HETEROCYCLES, AND DIENONES

by



PETER HANISCH

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH  
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THE UNIVERSITY OF ALBERTA  
FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend  
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CARBON-13 NMR: CONFORMATION ANALYSIS OF NITROGEN  
AND PHOSPHORUS HETEROCYCLES, AND DIENONES

submitted by PETER HANISCH

in partial fulfilment of the requirements for the degree of Master of  
Science in Chemistry.



*DEDICATION*

The Graduate Students and Postdoctoral Fellows of the  
Chemistry Department at the University of Alberta



## ABSTRACT

This treatise describes a study of the conformation of nitrogen and phosphorus heterocyclic compounds using carbon-13 nuclear magnetic resonance methods. Isolation and assignment of the configuration of the three diastereoisomers of 1,3,5-trimethyl-4-phenylpiperidin-4-ol and the conformational effects in 2,2,6,6-tetramethyl substituted piperidine rings are described. In addition, the possibility of detecting boat (non-chair) conformations in 4-phenylpiperidin-4-ol derivatives is discussed. A carbon-13 nmr solvent study of the model system, 3-piperidinol, was carried out to detect conformations where intramolecular hydrogen bonding interactions of the type  $-N\cdots H-O-$  are possible. Several 3-tropinone derivatives were studied and evidence is presented for boat (non-chair) conformations where similar  $-N\cdots C=O$  and  $-N\cdots H-O-$  interactions are implicated.

Several representative six-membered ring phosphorus heterocycles were also studied in both the PIII and PIV oxidation states. Evidence is presented for the predominance of axial phenyl groups in several 1-phenylphosphorinanes. Additivity effects were derived for the phosphorus systems and comparisons made with analogous nitrogen heterocyclic parameters. The effect of the PIV oxidation state upon the chemical shifts in the aromatic ring of various phenyl phosphine oxides and the consequent valence bond structure of these oxides is reported.

As a corollary, the chemical shifts of several dienones used as synthetic precursors in the above studies are reported and the effect of introducing a cross-conjugated double bond to the enone in acyclic and alicyclic systems is discussed.



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## CHAPTER ONE

### INTRODUCTION

#### A. Conformational Analysis of Non-Chair Structures - A Brief Review

Conformational analysis had its origins around the late 19th century when Sachse<sup>1</sup> suggested that cyclohexane could adopt two possible arrangements, later termed the 'chair' and 'boat' conformations. It is now well established that cyclohexane exists predominantly in the chair form, which is thermodynamically more stable than the boat. The boat conformer is destabilized by the presence of two eclipsed ethane type interactions and non-bonded interactions between the two 'flagpole' hydrogen atoms. Further, Hazebroek and Oosterhoff<sup>2</sup> have provided evidence, from a statistical mechanical study, that while the chair is rigid and unable to have any relative motion of the ring carbons without distortion of bond angles, the boat form has a considerable amount of such motion possible. This pseudorotation transforms the classical boat into a preferred twist or flexible form. Unequivocal choice between the two conformations is not possible due to the high mobility of such forms.

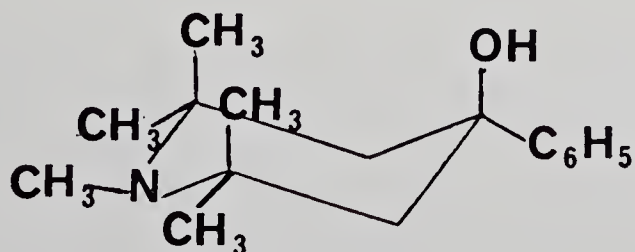
The question of non-chair structures contributing to the conformation of a variety of systems has subsequently been widely discussed<sup>3-24</sup>. It is informative to consider these contributions in their chronological order. Thus in 1951, Johnson<sup>3</sup> suggested that intramolecular interactions in several polycyclic molecules containing six-membered rings induce a preference for the boat conformation. However, it was not until 1957 that this feature was demonstrated by



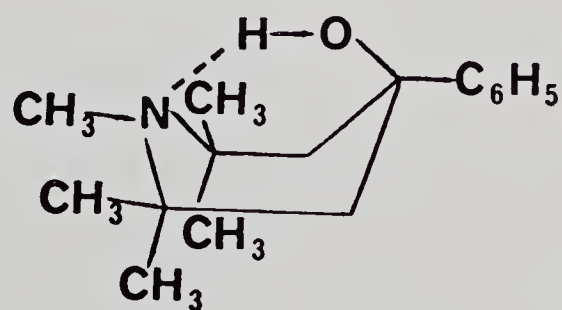
Barton and co-workers<sup>4</sup>. Two monobromo derivatives of lanost-8-en-3-one were obtained and their structures verified by chemical means.

Both had identical IR and UV absorption spectra characterizing an equatorial bromine substituent. Since it is impossible to have a pair of isomers for 2-bromolanost-8-en-3-one (1) having an equatorial bromine in a chair conformation it was concluded that ring A in the 2 $\beta$ -bromo-ketone should be in a boat form (Figure 1). The 1,3-diaxial interactions between the bromine atom and two methyl groups at C-4 and C-10 in the  $\beta$ -chair form can be relieved upon transforming to the boat conformer. Final verification was obtained in a pmr study by Abraham<sup>5</sup>. Since that time many other occurrences of boat conformations in steroidal systems have been reported<sup>6-9</sup>.

A study by Lyle<sup>10</sup> on the properties of 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol (2) revealed that acetylation was restricted compared with 1-methyl-4-phenyl-4-piperidinol. Further, the infrared absorption spectrum of the 1,2,2,6,6-pentamethyl system indicated intramolecular hydrogen bonding. The explanation offered considered the severe non-bonded interactions of the three axial groups in 2a compared with the stabilizing influence of hydrogen bonding in 2b thus favoring the boat conformation 2b.



2a



2b



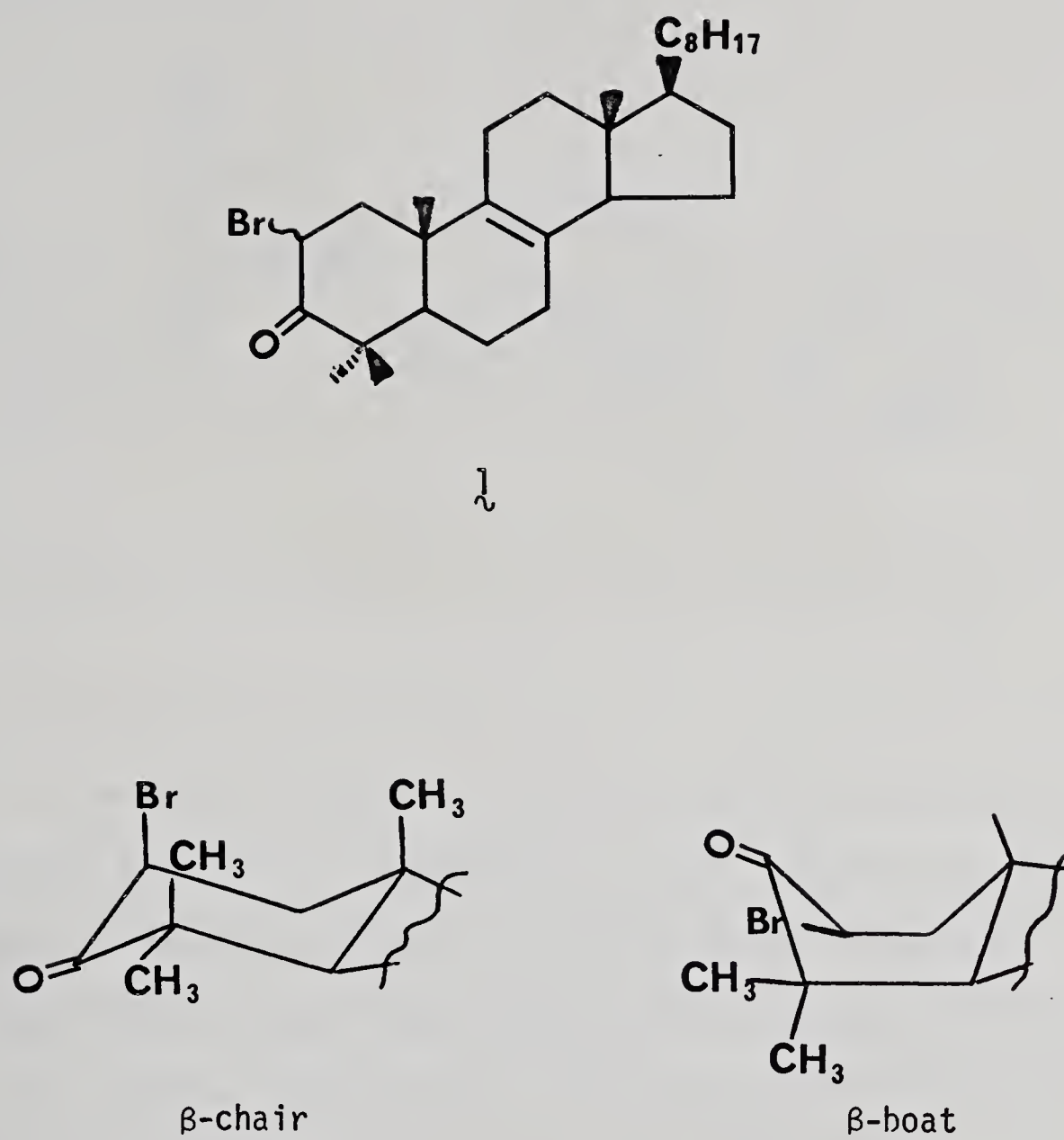
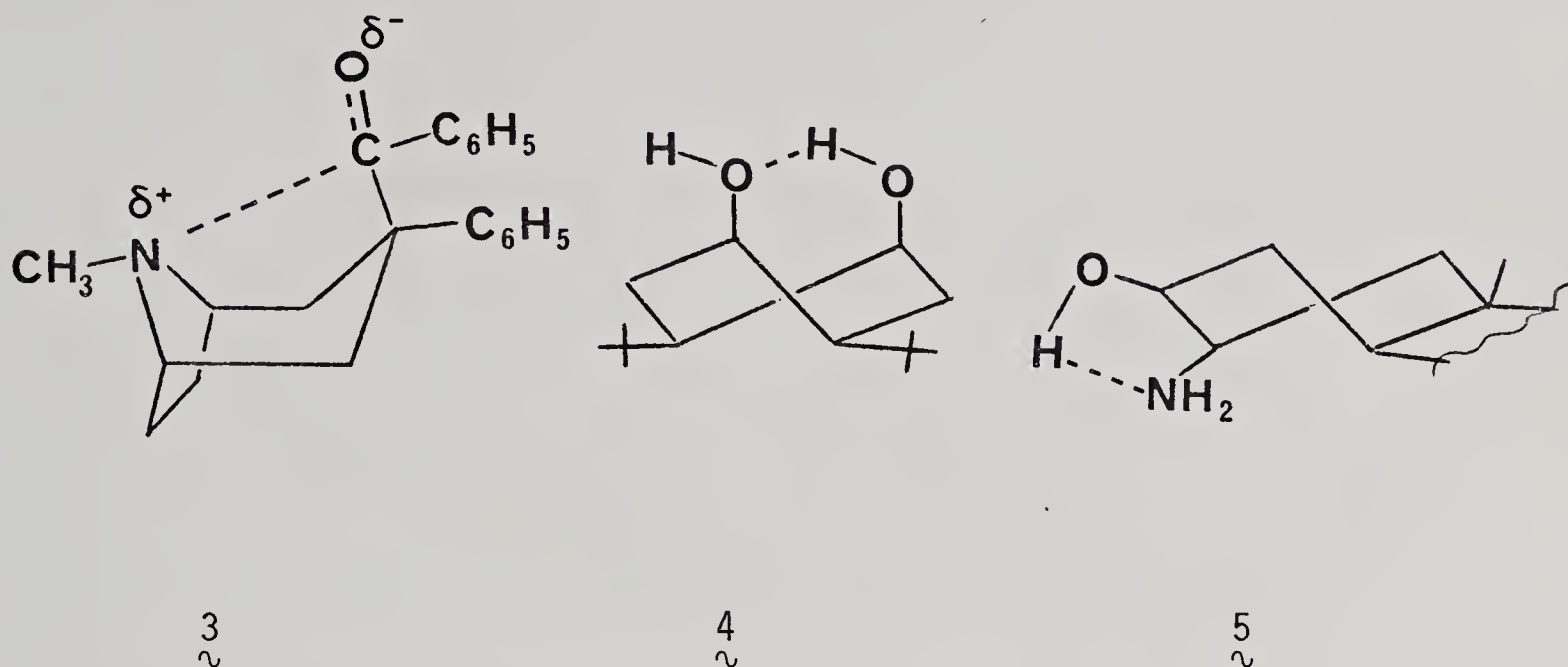


FIGURE 1:  $\beta$ -chair and  $\beta$ -boat forms of 2-bromolanost-8-en-3-one (1).



Other examples of this additional stabilization in the boat conformation are 3 $\alpha$ -phenyl-3 $\beta$ -tropanyl ketone (3)<sup>11</sup>, r-2-cis-5-di-t-butyl-cis-1,4-dihydroxycyclohexane<sup>12</sup> (4) and the A ring of 2 $\beta$ -amino-5- $\alpha$ -cholestan-3- $\alpha$ -ol (5)<sup>13</sup>.



A variety of attempts to classify molecules according to the factors which contribute to favouring non-chair conformations have been put forward. According to Kumler and Huitric<sup>14</sup> the six-membered ring system most likely to prefer boat conformations must meet two restrictions. 1) The ring possesses two or more atoms that are not sp<sup>3</sup> hybridized. 2) One atom in the ring is not sp<sup>3</sup> hybridized, and a strong dipole exists on the adjacent atom. The first case is exemplified by 1,4-cyclohexadiene, while an historically important though incorrect example<sup>15</sup> of the latter are the  $\alpha$ -halocyclohexanones.

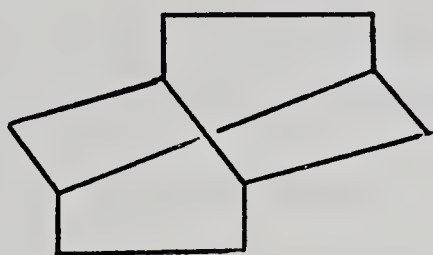
According to a recent review by Kellie and Riddell<sup>16</sup> non-chair conformations can be classified as follows:

- 1) Molecules constrained into non-chair forms by chemical bonding.
- 2) Molecules with an inherent preference for non-chair forms.



3) Molecules forced into non-chair forms by the magnitude of strain present in their chair conformations.

The first class contains such molecules as twistane (6) and bicyclo[2.2.2.]octane (7). These having a bridge constraining the structures into non-chair forms



6  
~



7  
~

The second class corresponds to the proposition of Kumlar and Huitric<sup>14</sup>, examples being 1,4-cyclohexadiene and the analogous dioximes. 1,4-Dimethylenecyclohexane<sup>17</sup> and its exo-tetramethyl analogs are also suggested to exist in a non-chair conformation, but X-ray studies<sup>18</sup> of the exotetracyano derivative indicate the chair form to be the most stable.

The third class represents the majority of non-chair conformations. A shift in conformational equilibrium from chair to boat could be more effective if unfavourable interactions present in the chair form are relieved during the interconversion. This is best exemplified by the trans-1,3 and cis-1,4-di-*t*-butylcyclohexanes. The severe non-bonded interactions of the *t*-butyl groups are removed upon conversion to the



twist conformer. In some molecules, not only are the interactions in the chair form eliminated but also stabilizing interactions such as intramolecular hydrogen bonding in the boat form, cause the latter conformer to be preferred as in  $\underset{\sim}{2b}$ ,  $\underset{\sim}{3}$ ,  $\underset{\sim}{4}$  and  $\underset{\sim}{5}$ .

The majority of common physical methods have been applied to study contributions made by non-chair conformations. These include X-ray<sup>19</sup>, ORD-CD<sup>20</sup>, IR and UV absorption spectroscopy<sup>21</sup>, dipole moments<sup>22</sup> and proton magnetic spectroscopy<sup>23,24</sup>. In the light of the success of the pmr investigations we elected to test the validity of using  $^{13}\text{C}$  magnetic resonance techniques in this area since it is clear that carbon-13 chemical shifts strongly reflect steric influences particularly important in the relief of syn-axial interactions in chair conformations and the introduction of flagpole interactions in boat forms.

In order to compliment the  $^{13}\text{C}$  study on the -N---H-O- and -N---C=O intramolecular hydrogen bonding type interactions as present in compounds  $\underset{\sim}{2}$  and  $\underset{\sim}{3}$  we used 3-hydroxypiperidinol as a model system. The -N---HO-interaction in this molecule is established<sup>25</sup>. A solvent study on the configurational equilibrium of this molecule using cmr can be discussed in relationship to the potential effects of hydrogen bonding on the chemical shifts of the piperidine ring carbons.

During the course of these investigations some approaches to the use of cmr to study non-chair structures have been reported<sup>26a,26b</sup>. In these examples, it is apparent that breakdown in accepted substituent additivity parameters provide the principal mechanism for describing conformational contributions from non-chair structures. We elaborate this feature in the following section.



## B. Carbon-13 Additivity Effects

An important aspect for the application of  $^{13}\text{C}$  data to structural and conformational elucidations, is the use of simple additivity relationships, correlating the shieldings within a closely related series of compounds with a number of structural parameters. This correlation was first noted by Lauterbur<sup>27</sup> and his proposal extended by Savitsky and Namikawa<sup>28</sup> and later in a most detailed study by Grant and co-workers<sup>29,30</sup>.

For linear hydrocarbons five parameters are necessary to define the shieldings. These are defined as  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$  and  $\epsilon$ , i.e. the shifts produced along the chain on that particular labelled carbon position on replacing a hydrogen atom with a substituent group. All of these parameters, with the exception of the  $\gamma$ -effect are paramagnetic, the gamma-gauche effect being diamagnetic. For example, in the alkanes the  $\alpha$ -effect  $\underline{\text{C}}\text{-H} \rightarrow \underline{\text{C}}\text{-X}$  causes a deshielding of  $\approx 9$  ppm, the magnitude varying between various families of compounds. The  $\beta$ -effect  $\underline{\text{C}}\text{-CH} \rightarrow \underline{\text{C}}\text{-CX}$  is similar in magnitude to the  $\alpha$ -effect. The  $\gamma$ -effect is a shielding effect (2.5 ppm)  $\underline{\text{C}}\text{-CCH} \rightarrow \underline{\text{C}}\text{-CCX}$ . This effect has important implications for stereochemical studies (vide infra). The  $\delta$  and  $\epsilon$  effects are quite small, +0.3 and +0.1 ppm, respectively, in this series.

The  $\alpha$ -effect can be explained by charge polarization effects<sup>31</sup>. Removal of electronic charge from the carbon by substituting a proton for a methyl group creates a small increase in effective nuclear charge of the remaining orbitals. Thus decreasing the average orbital radius causing the  $\langle r^{-3} \rangle_{2p}$  term of the Karplus-Pople equation<sup>32</sup> to be enlarged, hence a downfield shift.



$$\sigma_p = -\frac{e^2 h^2}{2m^2 c^2 \Delta E} \langle r^{-3} \rangle_{2p} \sum_B Q_{AB}$$

Cheney estimated<sup>31</sup> the change in the paramagnetic shielding constant,  $\sigma_p$ , to be less than 2 ppm for a molecule containing a  $\beta$ -methyl group and 0.5 ppm for a  $\gamma$ -methyl group. Hence it was suggested, that since the inductive effect does not significantly deshield the carbon position other than at the  $\alpha$ -position, that this does not serve as an explanation for the  $\beta$ - and  $\gamma$ -methyl substituent parameters. The latter were thought to be steric in origin. The steric interaction with the  $\beta$ -methyl causes a contraction of the orbitals of the atom of interest, hence resulting in a downfield shift. The  $\gamma$ -effect, exemplified by methylcyclohexane, follows from the possible steric polarization of electrons along the C-H bond at the  $\gamma$ -position due to non-bonded interactions across the ring such that the carbon nucleus is shielded and the attached protons are deshielded.

Further discussion of the  $\gamma$ - and  $\delta$ -effects is warranted since they are both used extensively in this research.

The  $\gamma$ -1,4 gauche-effect was recently reviewed by Pehk and Lippmaa<sup>33</sup> and Eliel and co-workers<sup>34</sup>. This diamagnetic effect was first mentioned by Grant and Paul in the alkane series<sup>30a,35</sup>, later for cyclohexane derivatives<sup>36</sup> and subsequently proposed<sup>36</sup> as a method for conformational analysis of such compounds but without any theoretical interpretation.

The  $\gamma$ -effect shows some regularities. It is diamagnetic and increases with decreasing interatomic distance between the 1 and 4 atoms



(Figure 2) but the number of interacting heavier atoms and not just the distance between them is important since the  $\delta$ -effect is usually deshielding even with short H---H interactions<sup>37</sup>.

The 1,4-interaction is not additive, in fact it is different for different nuclei, appearing also in spectra of  $^{15}\text{N}$ ,  $^{17}\text{O}$ ,  $^{19}\text{F}$  and  $^{31}\text{P}$ <sup>38</sup> and can even be unequal for the nuclei of the same type in different positions in the molecule.

An important contribution to the studies on the  $\gamma$ -effect was presented by Eliel and co-workers<sup>34</sup>: They observed that, while 2nd row heteroatoms (N, O, F) cause significant upfield shifts in the resonance of anti-periplanar carbon nuclei, a methyl or methylene group or 3rd row heteroatoms (S, Cl) demonstrate negligible (<1 ppm) anti effects. In fact a gauche heteroatom (Figure 2a) results in an upfield shift of the carbon-13 signal greater than the upfield shift caused by a methyl or methylene group. These authors proposed<sup>34</sup> the following mechanism to explain the unique role which N, O, and F play in the  $\gamma$ -anti shift. "Partial  $\pi$ -bond involvement of the free-electron pairs of these second-row elements is favoured by the shorter C-X bond and the more nearly similar radial dimensions of these atoms with that of carbon. Conversely Cl and S have larger covalent radii and less favourable radial matching with the  $p_\pi$  orbitals of carbon."

The deshielding  $\delta$ -1,5 interaction effect was first noted by Roberts<sup>39</sup> and its stereochemical dependence was later discussed by Stothers<sup>37</sup>. The  $\delta$ -groups may have various orientations as shown in Figure 3.

The  $\delta$ -effect is largest and most distinctive for molecules with the syn-axial orientations, generally being of the order of 2-3 ppm



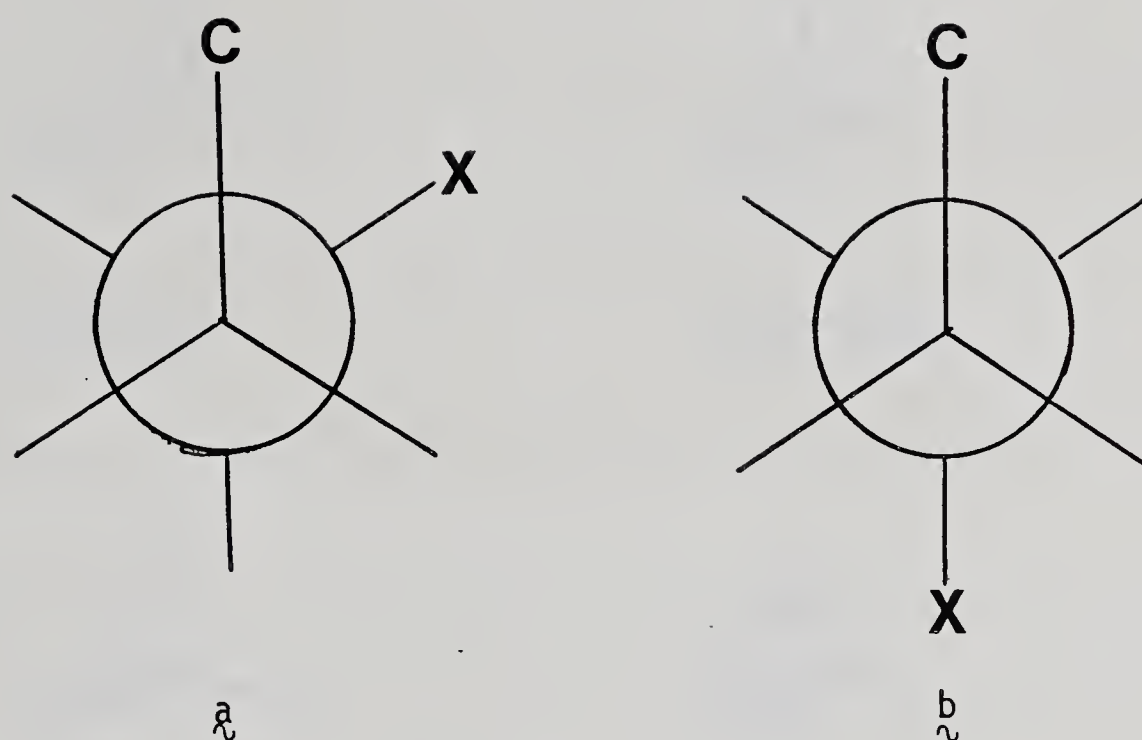
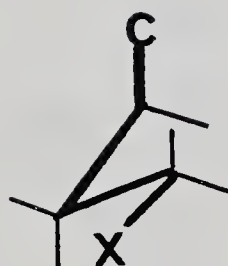


FIGURE 2: The  $\gamma$ -Effect:  $\gamma$ -gauche  $\tilde{a}$  or eclipsed arrangement produces an upfield shift of the carbon signal relative to the shielding of the corresponding carbon in the anti form  $\tilde{b}$ .

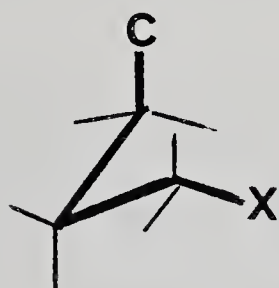




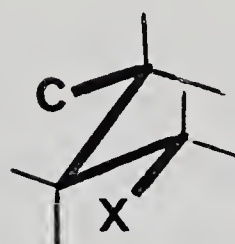
Syn-axial



Gauche-trans



Gauche-gauche

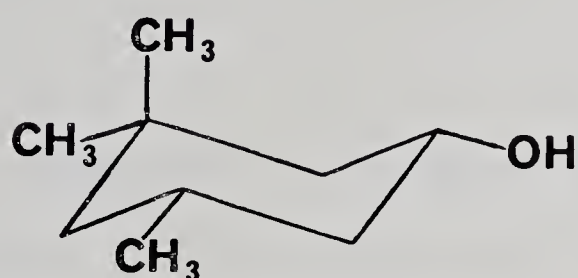


Trans-trans

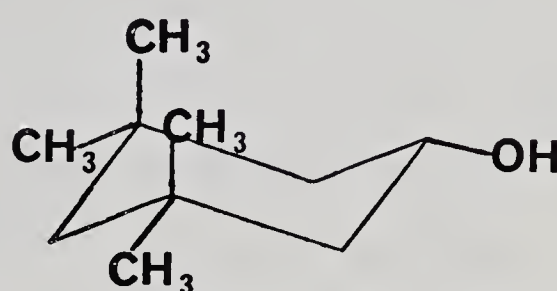
FIGURE 3: The  $\delta$ -Effect: The relative orientations of the  $\delta$ -groups C and X.



for non-rigid molecules<sup>37</sup> and as high as 6.6 ppm in rigid molecules<sup>37</sup>. The former can be exemplified by comparing structures 8 and 9.



8



9

The introduction of the extra methyl causes the C3' axial carbon in 8 to be deshielded by 2.1 ppm. In a rigid system the deshielding is more enhanced, the introduction of a methyl at the C-8 position in 1-methylnaphthalene causes the 1-methyl carbon to be deshielded by 6.6 ppm.

The gauche-trans and gauche-gauche  $\delta$ -effects are small, in the reported cases  $<1$  ppm. In fact, for two methylnorbornane derivatives a small shielding effect was observed. The trans-trans  $\delta$ -effect shown by exo-6-methyl-exo-2-norbornanol exhibits a 0.9 ppm shielding effect.

The deshielding effect appears to be more pronounced when there exists steric crowding of the  $\delta$ -groups, hence differing from the behaviour found for the  $\gamma$ -nuclei.

### C. Carbon-13 nmr in Conformational Analysis

Dalling and Grant<sup>30b,40</sup> have characterized the effect of



methyl substitution in a series of methylated cyclohexanes and aided by additivity parameters, obtained from the unequivocal assigned chemical shifts of certain derivatives, were able to assign the entire series with little ambiguity. At room temperature only average  $^{13}\text{C}$  chemical shifts are obtained while lowering of the probe temperature enables isolation of the individual spectra of the axial and equatorial conformers. The axial methyl carbon resonates 6 ppm to high field of the equatorial one. Further comparisons can be made by observing the shieldings for cis- and trans-4-t-butylcyclohexyl derivatives<sup>40,41</sup>. In general the equatorial substituent deshields the  $\alpha$ ,  $\beta$  and  $\gamma$  carbons relative to the effect of an axial group. As can be seen from the Karplus-Pople equation mentioned earlier the paramagnetic shielding parameter is directly dependent on the charge density, hence the chemical shift of the cyclohexane ring will depend on the substituent's electronegativity. Table I lists representative data for various cyclohexane substituents.

The carbon chemical shifts and conformational analysis of various nitrogen heterocycles has been described by several authors<sup>34,43-47</sup> and particular interest in those related to analgesic activity have been studied in our laboratory.

A particular area where pmr has proved to be useful has been in studies related to the nature of stereo-structural activity relationships in analgesically active components including derivatives of 4-phenylpiperidines<sup>48</sup> and 6,7-benzomorphans<sup>49</sup>. It has been established<sup>50,51</sup> that the analgesic potency of morphine and synthetic analgesics correlate with the attainment of a configuration in which the phenyl group is axially orientated. Casy and co-workers utilizing pmr identified the axial phenyl conformation in certain 4-phenylpiperi-



TABLE I

Substitution Effects<sup>a</sup> In Monosubstituted Cyclohexanes<sup>42</sup>

Substituent	$\alpha$	$\beta$	$\gamma$	$\delta$	% Axial
CH <sub>3</sub>	5.8	8.4	-0.5	-0.6	5
COOH	16.1	2.0	-1.4	-1.0	9
COOMe	15.8	2.0	-1.6	-1.2	10
NH <sub>2</sub>	23.5	10.1	-1.8	-1.1	12
OH	42.4	8.4	-2.6	-1.2	25
Cl	32.2	9.6	-2.4	-2.0	35
Br	25.0	10.3	-1.5	-2.0	35
I	4.2	12.2	-0.2	-2.1	33

<sup>a</sup>In ppm. Negative and positive values indicate upfield and downfield shifts, respectively.



dines<sup>48,52</sup> (i.e. promedol) and 3 $\alpha$ -phenyltropane-3- $\beta$ -carboxylate hydrochloride<sup>24</sup>. The latter, being the tropane analog of pethidine is more active an analgesic than its parent<sup>24</sup> and furthered the axial phenyl hypothesis for analgesic potency. In the latter study<sup>24</sup> a variety of similar tropane derivatives were described which were postulated to possess the -N---H-O- type intermolecular interactions discussed earlier. Hence we chose to use <sup>13</sup>C magnetic resonance methods in these systems to determine the value of <sup>13</sup>C nmr as a tool for conformational analysis of systems in which non-chair contributions were likely to be dominant, in particular, those systems involving intramolecular interactions.

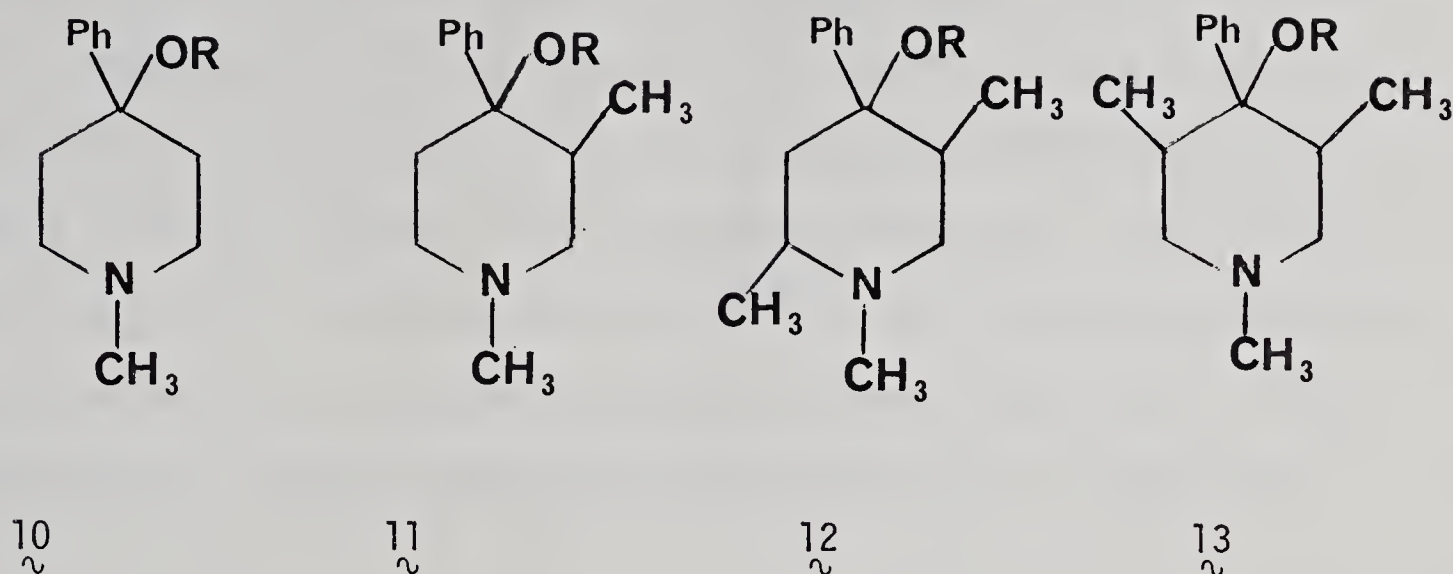
Further it should be mentioned that the non-chair conformation is a feature of particular importance in various pharmacological active molecules. Casy has proposed non-chair conformations for the active benzomorphan isomers<sup>49</sup> and the activity of certain ganglionic and neuromuscular blocking agents have been ascribed<sup>53</sup> to the steric crowding leading to chair deformations.

As a continuation of previous work in our laboratory on the potential of the <sup>13</sup>C magnetic resonance techniques as a tool in the determination of stereochemistry in analgesics<sup>43,54,55,56</sup> the conformation of the three diastereoisomers of 1,3,5-trimethyl-4-phenyl-4-piperidinols (13) have been determined in this study.

The 1,3-dimethyl-4-phenyl-4-piperidinols (11a) (the prodinols) and their corresponding propionate esters 11b (the prodines) have been investigated<sup>55</sup> along with the narcotic analgesic trimerperidine 12b, promedol, its isomers<sup>56</sup> and their precursors, 1,2,5-trimethyl-4-phenyl-4-piperidinols<sup>56</sup> 12a and the non-methylated 1-methyl-4-phenyl-4-



piperidinol derivatives<sup>55</sup> 10a, 10b.



a) R = H

b) R = CO Et

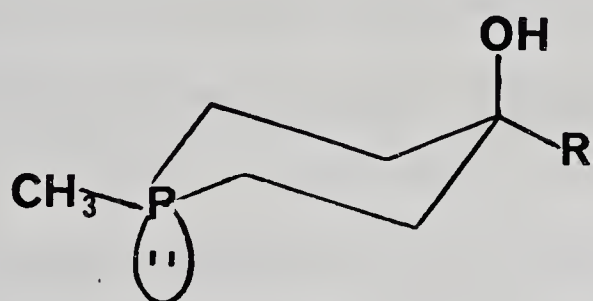
The establishment of the stereochemistry in all of the compounds 10, 11 and 12 was aided by use of empirical substituent parameters from carbon-13 studies of a series of substituted 4-piperidines<sup>43</sup> and 4-phenylpiperidines<sup>46</sup> of pharmacological interest. In particular, the clarification of the conflicting evidence<sup>52,57-59</sup> of the stereochemistry of the three isomers,  $\alpha$ ,  $\beta$  and  $\gamma$  of 12b involved the reversal of the prior assignment of the  $\beta$  and  $\alpha$  isomers and hence prompted the study of the  $\alpha$ ,  $\beta$  and  $\gamma$  isomers of 13a.

#### D. Phosphorus Heterocycles

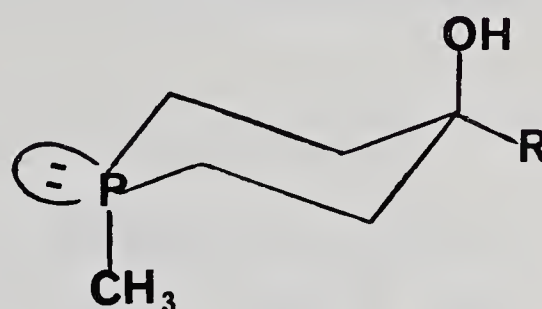
In contrast to the numerous studies available concerning the conformation of six-membered ring heterocyclic compounds containing O, N or S very little attention has been paid to the corresponding tervalent phosphorus system. Only in the past few years have workers turned to this challenging problem<sup>60-81</sup>.



The configurational stability for tervalent phosphorus, having a high barrier to inversion, has been demonstrated by Quin and co-workers<sup>60,61</sup> in isolating the cis- and trans-isomers of various phosphorus heterocycles. It is therefore interesting to compare the conformational stabilizing influence of phosphorus compared with the freely inverting nitrogen atom in analogous compounds. Thus, in the 1-methyl-4-alkyl-4-phosphorinanol  $\mathbf{14}$ <sup>60,61</sup> a configurational difference was observed at the phosphorus atom for the two isomers while in the corresponding nitrogen system only one diastereomer is observable.



$\mathbf{14}$ -cis



$\mathbf{14}$ -trans

Little preference for either equatorial or axial configuration of the P-CH<sub>3</sub> group is evident. (cis:trans >0:30).

Predominance of an axial phenyl group at the phosphorus atom in 1-phenyl-4-phosphorinanone  $\mathbf{15}$  and its dimethyl ketal  $\mathbf{16}$  is shown in the solid state by X-ray analysis<sup>62</sup>. Earlier Albrand et al.<sup>63a</sup> developed a relationship between  $^2J_{\text{PCH}}$  and the dihedral angle  $\alpha$  and assigned the solution conformation of  $\mathbf{15}$  as a chair or possibly a boat, with the phenyl group equatorial. However, taking into consideration the X-ray data Quin suggests<sup>62</sup> that Albrand's calculations may be in error.

Recently the axial preference for phosphorus substituents in



six-membered rings has been reported for alkyl (except *t*-butyl) and aryl groups in 2-phospha-1,3-dioxas<sup>64</sup> and 2-phospha-1,3-dithiacyclohexanes<sup>65</sup> and for various substituents ( $Z = \text{Cl}, \text{OCH}_3, \text{CH}_3, \text{iPr}$  and  $\text{Ph}$ ) in 5-*t*-butyl-2( $Z$ )-1,3,2-dioxaphosphorinanes<sup>66,67</sup> in predominantly chair conformations. Further, Lambert *et al.*<sup>68</sup> have shown that the proton on phosphorinane prefers the axial orientation. The axial preference in these systems has been attributed to favourable P and O lone-pair interactions<sup>67</sup> influencing the torsional barrier of the phosphorus or the possibility that the syn-axial interactions may be greatly reduced<sup>66</sup> since the phosphorus-oxygen bonds are considerably longer than the carbon-oxygen bonds and because of possible consequent flattening of the ring about phosphorus.

There are distortions from cyclohexane geometry in the phosphorinane compounds, the P-C bond being 0.33 Å longer than the C-C bond, the  $\angle \text{CPC}$  bond angle used for discussions taken as  $100^\circ$ <sup>69</sup>. The widening of the ring around phosphorus increases the puckering at C-4, the axial substituent at this position being projected slightly towards the ring. Hence conversion of a chair form, with an equatorial P-substituent into its boat conformer causes severe flagpole-bowsprit interactions, this not being the case with an axial P-substituent.

High resolution  $^1\text{H}$  and  $^{31}\text{P}$  nmr have been employed<sup>70a-d</sup> for structural determination of organophosphorus compounds. However, in most cases the  $^{31}\text{P}$  spectra give rise to only one chemical shift parameter. This, together with the fact that the proton signals occur in a very narrow range and are thus difficult to assign suggests that  $^{13}\text{C}$  nmr studies would be valuable.

During the course of this work several reports have appeared



concerning  $J_{CP}^{71-77}$  coupling constants obtained from direct measurement of the  $^{13}C$  nmr spectra of selected alicyclic<sup>71,72</sup>, acyclic<sup>73,74</sup> and heteroaromatic<sup>75,76,77</sup> phosphorus derivatives. Evidence has been presented<sup>74,78-81</sup> that clearly shows a dependence of both  $J_{C-P}^{13-31}$  coupling constants and  $^{13}C$  chemical shift on structures in these compounds and thus our overlapping efforts have been supplemented by these results. Our efforts have been particularly related to the synthesis of phosphorus analogs of the nitrogen heterocycles described earlier. However, due to problems of compound stability only the phenyl analogs in the phosphorinanone compounds and derivatives were studied in detail. Supplementary data on the cyclic phosphines and their corresponding oxides are described. Some insight into the  $\pi$ -bonding in the P-O bond has been gained (compare ref. 82).

#### E. Carbon-13 Chemical Shifts of Selected Dienones

The nitrogen and phosphorus heterocyclic compounds described in this work were synthesized by amine or phosphine:dienone condensation. Since there is a paucity of data concerning the carbon chemical shifts of cross-conjugated ketones, phorone and pipertenone being the only examples<sup>23</sup>, we elected to determine the  $^{13}C$ -chemical shifts of the dienones. These results are described in Chapter V.

#### F. $^{13}C$ NMR: Principles of Data Acquisition

Proton magnetic resonance has grown into one of the most important methods of instrumental analysis routinely used by organic chemists. Nevertheless it is limited for two reasons. First, the physical properties and reactivity of organic compounds are more



effectively explained by the carbon atoms and their bonding states than the protons. Secondly, many organic molecules give rise to extremely complex proton spectra covering a small range ( $\sim 10$  ppm). The  $^{13}\text{C}$  nuclei on the other hand absorb over a wide range of approximately 220 ppm and the  $^{13}\text{C}$  spectra, routinely recorded with complete proton decoupling (vide infra) consist of single resonances (providing other magnetic nuclei are absent) for each individual carbon atom in the molecule.

The application of nmr to the  $^{13}\text{C}$  isotope has two drawbacks. 1) Its low natural abundance (1.1%) and, 2) its low sensitivity, 1.6% compared to  $^1\text{H}$  resonances (100%) at the same magnetic field strength. The techniques for overcoming these difficulties have been reviewed in detail by Levy<sup>84</sup>, Stothers<sup>85</sup> and Breitmaier<sup>86</sup>. We therefore describe the technique relevant to this present work, pulsed Fourier Transform NMR (PFT).

PFT nmr differs from the conventional steady-state experiment (continuous wave CW) in that the sample is irradiated with the pulse exciting all nuclei simultaneously away from their equilibrium orientation with the magnetic field, so generating a signal that, after the pulse, decays through relaxation processes ( $T_1$ ,  $T_2$ ) to zero and equilibrium is re-established. This free induction decay (FID) is the Fourier Transform of the steady state resonance<sup>87</sup>.

Each FID is stored and accumulated in the computer memory and the spectrum is extracted by taking the inverse F.T. since the original signal, a modulated exponential decay, contains all of the information in the normal absorption pattern. Time averaging a series of FID signals provides a S/N ratio (signal to noise) enhancement of  $\sqrt{n}$  with the added feature that the repetition rates can be much higher



than in the steady state operation. This leads to an additional improvement of up to 100 fold for a comparable sample time. One of the limiting factors in the experiment is the relaxation time of the resonance signals. The pulse repetition rate must be longer than the  $T_1$  (spin-lattice relaxation time) for the resonances so that equilibrium can be re-established between successive pulses. In the PFT  $^{13}\text{C}$  nmr experiment a heteronuclear lock signal, usually the  $^{19}\text{F}$  signal of hexafluorobenzene or the  $^2\text{H}$  signal of a deuterated solvent  $\text{CDCl}_3$ ,  $\text{C}_6\text{D}_6$ , etc. is used to stabilize the field.

### :Spectral Interpretation

'Off-resonance' proton decoupling is a technique which is a routine experiment to determine the kind of carbon substituents. The method involves placing an attenuated decoupling frequency outside the range of the Larmour frequencies of the protons, approximately 500 Hz from the optimal decoupling value. Hence, vicinal and long range couplings collapse and the characteristic first order splitting patterns for  $\text{CH}_3$ ,  $\text{CH}_2$ ,  $\text{CH}$  and quaternary carbons; quartet, triplet, doublet and singlet respectively, are readily discernible with residual couplings,  $J_r$ . The off-resonance spectrum suffers only a small decrease in S/N. In practice, quaternary carbons are detected since their signals are not affected by the decoupling frequency. Methyl and methine carbons are identified by the absence of a signal at the same position in both the decoupling and off-resonance spectra while a methylene carbon gives rise to a triplet centered at the position of the peak in the decoupled spectrum.

As a consequence of carbon-13 relaxation being dominated by proton-carbon dipole-dipole coupling, a carbon atom not directly bonded



to a proton is expected to give rise to a spectral line of lower intensity than the maximum possible from dipole-dipole relaxation (Nuclear Overhauser effect). Hence, this can be indicative of quaternary resonances present in the spectrum. Further proof of these resonance assignments can be obtained by a modulated off-resonance experiment in which the irradiation frequency is offset as before but the signal is modulated, thus effectively irradiating weak and small couplings, the quaternary resonances being 'decoupled' appear as sharp singlets.

A great asset of the spin decoupling technique arises from knowledge of the fully analyzed proton spectrum. That is, the carbon-13 spectrum may be assigned by directly relating each carbon resonance with an assigned proton resonance position by selective decoupling<sup>88</sup>. The experiment consists of aligning the decoupling frequency at the center of the multiplet of the protons directly bonded to the carbon atom to be assigned. Given a sufficiently spread out proton spectrum only the resonance due to the directly bonded carbon atom will be decoupled giving a single resonance whereas the other carbon atoms will remain coupled.

All of these techniques have been employed in the present work in order to establish spectral assignments.

## G. Experimental

Carbon-13 nmr spectra were determined using a Bruker HFX-90 spectrometer operating at 22.63 MHz in conjunction with a Nicolet-1085, 20K memory, computer. The instrument consists of a deuterium lock system, a BSV-2 random noise (800 Hz band-width) proton decoupler and a BSV-2 pulse generator-amplifier. All samples were contained in



precision ground 10 mm, o.d., tubes. The spectrometer was used in the crosscoil configuration. On the average a 8  $\mu$ s pulse, corresponding to an approximate tilt angle of  $45^\circ$ , was employed. The delay between pulses was 0.8 sec. for the average spectral width of 5000 Hz. Accumulation time averaged 30 mins. over 8K data points for concentrations of the order of 0.27 M. For off-resonance on coupled spectra this time was doubled. All carbon chemical shifts reported in this work are given in parts per million downfield from TMS. Hence a negative chemical shift parameter refers to an upfield shift, and a positive value, a downfield shift.

The pmr spectra were recorded using Varian Associates 60 or HA-100 spectrometers.

The experimental procedures for obtaining the compounds used in this work are reported at the end of the relevant chapter.



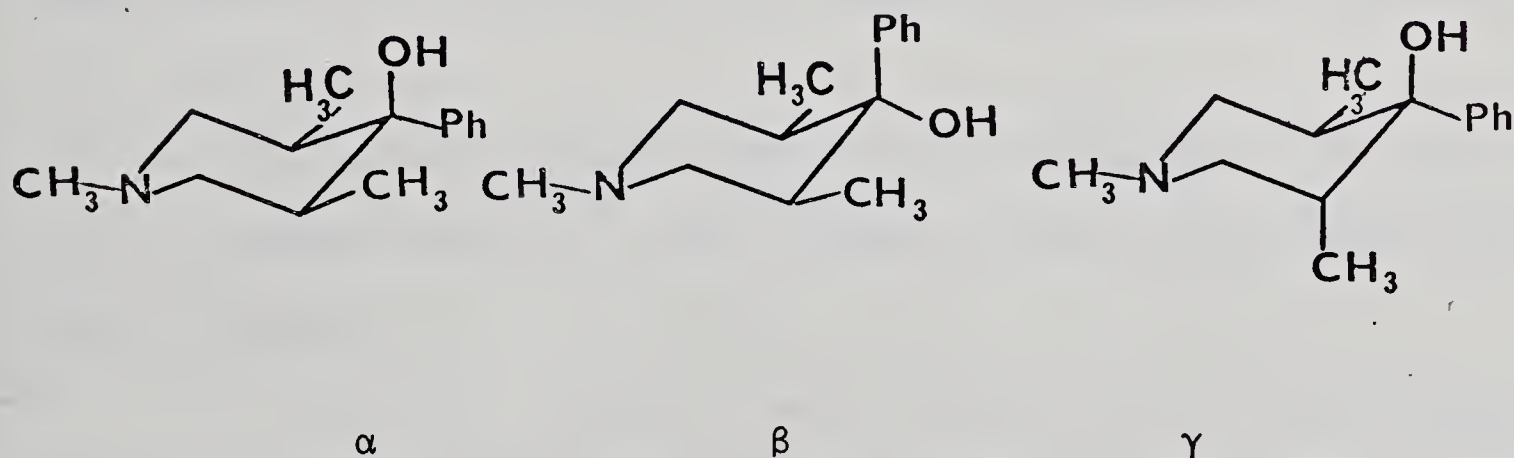
## CHAPTER TWO

### NITROGEN HETEROCYCLES

#### A. The Stereochemistry of 1,3,5-Trimethyl-4-piperidone and its 4-Phenylalcohol Derivatives

##### INTRODUCTION

The isolation of the three isomeric 1,3,5-trimethyl-4-phenyl-4-piperidinols from a phenyllithium reaction on the corresponding ketone has been described by Sorokin<sup>89</sup>. The structures of the three isomers were assigned as  $\alpha$ ,  $\beta$  and  $\gamma$  on the basis of the ease of esterification. No spectral evidence was reported.



Sorokin also showed that the propionic ester hydrochlorides of the  $\alpha$ - and  $\beta$ -isomers (cis Me-Me) were analgesically inactive, while the ester hydrochlorides of the  $\gamma$ -isomer (trans Me-Me) was as potent as promedol (See Chapter One). It was suggested that the inactivity of the cis-isomers may be due to the equatorial methyl groups hindering the formation of a drug-receptor complex. The inverted chair form of the  $\gamma$ -isomer



in which the phenyl group is axially orientated occurs only to the extent of 15%<sup>90</sup>. The active conformer therefore, has an equatorial phenyl group consequently defying the "axial-phenyl configuration requirement" described in Chapter One.

Since carbon-13 nmr studies<sup>56</sup> carried out in this laboratory had shown that the conformations of the four diastereoisomers in the analogous 1,2,5-trimethyl (promedol) derivatives were previously assigned incorrectly, it seemed desirable to repeat Sorokin's synthesis and to determine the conformation of the  $\alpha$ ,  $\beta$  and  $\gamma$ -1,3,5-isomers unequivocally using <sup>13</sup>C nmr methods.

## RESULTS

The conventional labelling system for the piperidine ring is employed throughout this work. Carbon atoms in substituents are identified by a prime symbol for the number appropriate to the position of substitution on the piperidine ring. Phenyl ring carbons are labelled C-q, C-o, C-m and C-p.

The carbon-13 chemical shifts of 1,3,5-trimethyl-4-piperidone 17, its 4-phenylalcohol,  $\alpha$ ,  $\beta$  and  $\gamma$ -isomers and their hydrochlorides are given in Table II.

In the above compounds symmetry exists in all but the  $\gamma$ -isomer, in which the methyl groups are axial and equatorial at C-3 and C-5, respectively. In the  $\alpha$ - and  $\beta$ -isomers the double intensity of the resonances due to the equivalent carbons C-2,6, C-3,5 and C-3',5' enable their distinction compared to the single intensity of the resonances due to C-1' and C-4. Typical low field shifts for a carbonyl resonance ( $\sim 200$  ppm) distinguish the C-4 carbonyl carbonyl, while in the phenylalcohol isomers the C-4 resonance was identified using modulated



TABLE II

Carbon-13 Chemical Shifts<sup>a</sup> of 1,3,5-Trimethyl-4-piperidone, the  $\alpha$ -,  $\beta$ - and  $\gamma$ -4-phenyl-4-ol Derivatives and their Corresponding Hydrochlorides

Compound	Carbon Position											
	C-2	C-3	C-4	C-5	C-6	C-1'	C-3'	C-5'	C-q	C-o	C-m	C-p
17	64.3 <sub>5</sub>	43.6 <sub>9</sub>	210.6 <sub>6</sub>	43.6 <sub>9</sub>	64.3 <sub>5</sub>	45.0 <sub>4</sub>	11.4 <sub>3</sub>	11.4 <sub>3</sub>				
17a	60.4 <sub>2</sub>	41.0 <sub>5</sub>	205.2 <sub>1</sub>	41.0 <sub>5</sub>	60.4 <sub>2</sub>	43.2 <sub>6</sub>	10.9 <sub>5</sub>	10.9 <sub>5</sub>				
C17a <sup>‡</sup>	59.5 <sub>1</sub> (57.5 <sub>2</sub> )	41.0 <sub>5</sub> (39.2 <sub>8</sub> )	209.2 <sub>1</sub> (93.0 <sub>1</sub> )	41.0 <sub>5</sub> (39.2 <sub>8</sub> )	59.5 <sub>1</sub> (57.5 <sub>2</sub> )	43.3 <sub>3</sub>	10.3 <sub>2</sub> (9.5 <sub>0</sub> )	10.3 <sub>2</sub> (9.5 <sub>0</sub> )				
α	58.9 <sub>1</sub>	40.8 <sub>3</sub>	75.9 <sub>6</sub>	40.8 <sub>3</sub>	58.9 <sub>1</sub>	46.1 <sub>2</sub>	12.2 <sub>4</sub>	12.2 <sub>4</sub>	145.6 <sub>0</sub>	128.0 <sub>7</sub>	126.3 <sub>4</sub>	125.1 <sub>6</sub>
α·HCl	55.8 <sub>3</sub>	38.7 <sub>9</sub>	74.6 <sub>1</sub>	38.7 <sub>9</sub>	55.8 <sub>3</sub>	43.4 <sub>3</sub>	11.9 <sub>8</sub>	11.9 <sub>8</sub>	142.9 <sub>6</sub>	128.2 <sub>3</sub>	126.9 <sub>4</sub>	124.5 <sub>8</sub>
β	60.2 <sub>6</sub>	43.9 <sub>7</sub>	76.6 <sub>6</sub>	43.9 <sub>7</sub>	60.2 <sub>6</sub>	45.6 <sub>9</sub>	13.2 <sub>7</sub>	13.2 <sub>7</sub>	141.5 <sub>6</sub>	127.7 <sub>4</sub>	127.3 <sub>1</sub>	126.5 <sub>0</sub>
β·HCl	57.9 <sub>4</sub>	41.2 <sub>1</sub>	74.5 <sub>0</sub>	41.2 <sub>1</sub>	57.9 <sub>4</sub>	43.6 <sub>4</sub>	12.5 <sub>2</sub>	12.5 <sub>2</sub>	139.2 <sub>4</sub>	129.4 <sub>2</sub>	128.2 <sub>3</sub>	127.2 <sub>6</sub>
γ	58.4 <sub>8</sub>	42.1 <sub>9</sub>	76.2 <sub>8</sub>	31.5 <sub>0</sub>	59.4 <sub>5</sub>	46.5 <sub>6</sub>	16.6 <sub>2</sub>	12.8 <sub>4</sub>	145.4 <sub>9</sub>	128.0 <sub>2</sub>	126.7 <sub>7</sub>	126.3 <sub>4</sub>
γ·HCl	56.2 <sub>1</sub>	41.0 <sub>5</sub>	74.9 <sub>7</sub>	30.1 <sub>6</sub>	56.2 <sub>1</sub>	44.5 <sub>6</sub>	15.9 <sub>7</sub>	12.5 <sub>9</sub>	143.0 <sub>6</sub>	128.2 <sub>8</sub>	126.4 <sub>5</sub>	127.4 <sub>7</sub>

<sup>a</sup> Given in ppm downfield from TMS. Solvent: CDCl<sub>3</sub> except  $\neq$  D<sub>2</sub>O.

<sup>b</sup> Values in parenthesis are approximately 10% the intensity of the parent resonance.

<sup>c</sup> Original data converted using  $\delta_c^{\text{Dioxane}} = 66.74$  ppm.



off-resonance methods. An off-resonance decoupled spectrum exhibited a characteristic triplet pattern about the lower field resonance and a doublet for the methine carbon resonance (40-43 ppm). Quartets about the highest field resonances (10-13 ppm) defined the C-3',5' methyl carbon atoms.

For the aromatic carbon atoms, the assignment of the quaternary and para resonances were distinguished by their lower intensity compared with the ortho and meta carbons. Distinction between the former pair was achieved by off-resonance decoupling. Ambiguities still remain for the assignments of the C-o and C-m atoms in all cases. However, the lower field resonance was assigned to the ortho position comparable to previous assigned 4-phenyl-4-piperidinols<sup>55,56</sup>.

For the  $\gamma$ -isomer and its hydrochloride salt the absence of symmetry gives rise to equally intense resonances for all of the ring carbon atoms. Off-resonance and modulated off-resonance techniques enabled distinction of C-4, the quaternary carbon atom and the methyl, methylene and methine carbons. The actual assignments were made through consideration of substituent parameters and trends observed upon protonation as described by Jones and co-workers<sup>43,55,56</sup>.

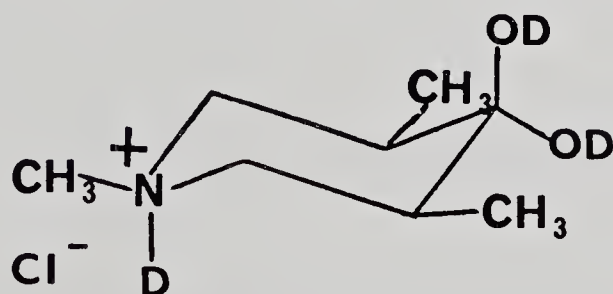
## DISCUSSION

Comparison of the carbon-13 chemical shifts of 1,3,5-trimethyl-4-piperidone and 1,3-dimethyl-4-piperidone<sup>55</sup> enables determination of the substituent effects of the equatorial methyl group ( $\alpha + 3.1$  ppm,  $\beta + 8.1$  ppm). These values compare favourably with those determined by Jones and Hassan<sup>43</sup> (+3.7 and +7.9 ppm, respectively) for piperidine rings. The  $\beta$ -effect of the equatorial methyl on the carbonyl resonance causes a downfield shift of 2.9 ppm. This difference in  $\beta$ -effects was also



noted by Jones and Hassan and attributed to the compensating effect of the carbonyl oxygen atom.

The pmr spectrum of the 4-piperidone hydrochloride salt was determined in both  $\text{CDCl}_3$  and  $\text{D}_2\text{O}$ . In the former, the N-methyl signal appeared as a doublet ( $J_{\text{HH}} = 7 \text{ Hz}$ ) centered at  $2.9_3$  ppm and the ring methyl appeared as a doublet ( $J_{\text{HH}} = 6 \text{ Hz}$ ) centered at  $1.0_9$  ppm. In the latter there was no change in the ring methyl shift but the N-methyl was a singlet at  $3.1_1$  ppm due to deuterium exchange of the N-H proton with the solvent. A further example of coupling of the N-methyl signal in  $\text{CDCl}_3$  solvent was observed in the pmr spectra of the  $\alpha$ ,  $\beta$  and  $\gamma$  hydrochloride derivatives (Table III). The carbon-13 spectrum of the hydrochloride  $17a$  determined in  $\text{D}_2\text{O}$  gave duplicate resonances for C-2,6, C-3,5 and C-3',5' carbon atoms. The "new resonances" accounted for about 10% of the total concentration and are attributable to the 4,4-dideuteroxy form of  $17a$  since a concomitant resonance was observed at 93 ppm typical of a dihydroxy substituted carbon (C-4). Other examples



$17a$   
~

of hydration of the C-4 carbonyl group has been reported by Casy and Hassan<sup>91</sup> for the hydrochloride salt of 1,2,5-trimethyl-4-piperidone.



TABLE III

Proton Chemical Shifts<sup>a</sup> and Coupling Constants<sup>b</sup> of the N-Me  
and C-Me Protons in the  $\alpha$ ,  $\beta$  and  $\gamma$  Free Bases and  
Hydrochlorides

	N-Me	C-Me
$\alpha$	2.3 <sub>0</sub>	0.5 <sub>7</sub> (6.0 Hz)
$\alpha \cdot \text{HCl}$	2.8 <sub>5</sub> (5.0 Hz)	0.6 <sub>7</sub> (5.5 Hz)
$\beta$	2.3 <sub>9</sub>	0.6 <sub>3</sub> (6.5 Hz)
$\beta \cdot \text{HCl}$	3.0 <sub>4</sub> (4.5 Hz)	0.7 <sub>8</sub> (6.5 Hz)
$\gamma$	2.2 <sub>7</sub>	0.7 <sub>6</sub> (6.5 Hz) eq; 0.8 <sub>2</sub> (7.3 Hz) ax.
$\gamma \cdot \text{HCl}$	2.8 <sub>3</sub> (5.0 Hz)	0.9 <sub>0</sub> (4.5 Hz) eq; 1.1 <sub>0</sub> (8.0 Hz) ax.

<sup>a</sup> Given in ppm downfield from TMS. Solvent  $\text{CDCl}_3$ .

<sup>b</sup> Values in parenthesis.



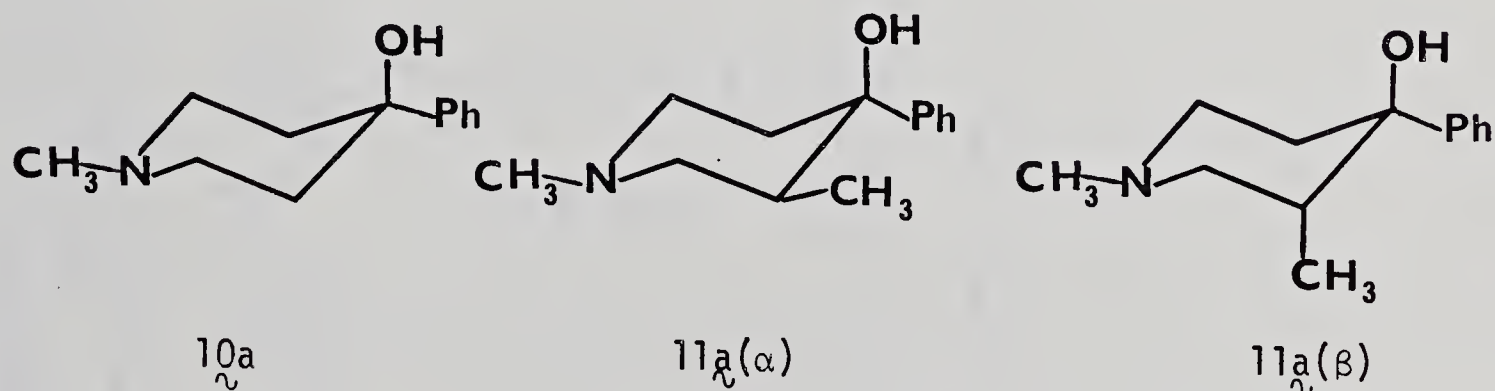
The configuration of the  $\alpha$ -isomer is identical to that proposed by Sorokin. The single resonance at 12.2<sub>4</sub> ppm characterises the equatorial ring methyl groups<sup>56</sup>. The C-q aromatic carbon at 145.6<sub>0</sub> ppm compares with the equivalent carbon in the  $\alpha$ -isomer of 1,3-dimethyl-4-phenyl-4-piperidinol<sup>55</sup> (147.5 ppm) if one considers the additional  $\gamma$ -shielding effect of the C-5 methyl group. In the 1,3-dimethyl system the phenyl group is established as having the equatorial orientation.

In the  $\beta$ -isomer the C-3,5 and C-3',5' carbon positions are deshielded by 3.1 ppm and 1.1 ppm, respectively, compared to the  $\alpha$ -isomer. Similar effects (+3.0 and +2.4 ppm) were observed at the analogous C-5 and C-5' carbon positions in the  $\beta$ -isomer of the 1,2,5-trimethyl-4-phenylpiperidin-4-ol<sup>56</sup> (12) in which the phenyl group is established as axial. The configuration of the phenyl group is defined by the shift of the phenyl C-q carbon. In the 1,2,5-trimethyl and 1,2-dimethyl-4-phenylpiperidin-4-ols this carbon is shielded by 2.3 and 3.8 ppm, respectively, compared to the isomer where the phenyl group is equatorial. In the 1,3,5-trimethyl,  $\beta$ -isomer the effect is similar in magnitude (-4.0 ppm). The similarity in the effects on the phenyl C-q carbon in the 1,2- and 1,3,5-isomers suggests similar conformations for these compounds. The attenuated value in the 1,2,5-isomer is attributed to a change in the relative orientation of the phenyl ring (vide infra). There is a noticeable difference in the substitution effects between the axial hydroxyl and axial phenyl groups on the C-2 and C-6 carbons in the 1,2-isomers; +1.4 and +0.2 ppm, respectively (axial phenyl has C-2 and C-6 to low field). However this cannot be attributable to methyl substitution since the analogous effect in the 1,3,5-isomer at C-2,6 is +1.4 ppm. Similar shieldings occur in the 1,2,5-isomer, +2.5 ppm (C-2)



and +0.4 ppm (C-6) with an enhanced effect at C-2 compared to the 1,2-isomer. It is suggested that the difference in the deshieldings at the C-2 and C-6 positions in the 1,2- and 1,2,5-isomers is due to the relative orientation of the phenyl ring with respect to these carbons. The deshielding being due to a  $\delta$ -effect caused by the interaction of the C-2 and C-6 carbons with the C-o aromatic carbons. The enhanced deshielding at C-2 in the 1,2,5-isomer is attributable to a change in phenyl orientation so as to cause a greater interaction between the C-o and C-2 carbons. The  $\delta$ -effect also accounts for the deshieldings of the C-5' methyls in the 1,2,5- and 1,3,5-isomers mentioned earlier.

The assignment of the  $\gamma$ -isomer was aided by the empirical additivity relationships derived from compounds  $10a$  and  $11a(\alpha)$ , i.e.  $\alpha + 2.4$ ,  $\beta_{C-q} + 3.3$ ,  $\beta_{C-2} + 7.4$  ppm<sup>55</sup> and applied to  $11a(\beta)$ .



The calculated shifts agree well (Table IV) for the C-4 and C-6 carbon atoms but deviate by 2.4 ppm at C-5. Evidently, there is no  $\alpha$ -effect, the shifts in both  $11a(\beta)$  and  $\gamma$  being 31.50 ppm. This effect presumably arises from a 1,4-gauche interaction between the phenyl ortho carbons on



TABLE IV

The Carbon-13 Chemical Shifts<sup>a</sup> of 1-, 1,3(ax)-, 1,3(eq)-, 1,3(ax),5(eq)- and 1,3(ax),5(eq)-Trimethyl-4-phenylpiperidin-4-ols.the *r* Hydrochlorides and the Derived Equatorial Methyl Additivity Parameters

Carbon Position	10a 	11a(α) <sup>c</sup> 	α 	11a(β) <sup>c</sup> 	χ 	Structure <sup>d</sup> and Additivity Parameters <sup>b</sup>	Δ <sup>b</sup> ppm	Δ <sup>b</sup> ppm	11a(α)·HCl <sup>c</sup> 	Δ <sup>b</sup> ppm	11a(β)·HCl <sup>c</sup> 	Δ <sup>b</sup> ppm	χ·HCl 	Δ <sup>b</sup> ppm
C-2	51.6 <sub>9</sub>	59.0 <sub>8</sub>	58.9 <sub>1</sub>	58.1 <sub>4</sub>	58.4 <sub>8</sub>	~0δ	~0δ	56.3 <sub>8</sub>	55.8 <sub>3</sub>	56.1 <sub>7</sub>	56.2 <sub>1</sub>	~0δ		
C-3	38.3 <sub>6</sub>	40.7 <sub>9</sub>	40.8 <sub>3</sub>	40.2 <sub>3</sub>	42.1 <sub>9</sub>	+2.0γ	+1.0γ	37.8 <sub>2</sub>	38.7 <sub>9</sub>	39.5 <sub>0</sub>	41.0 <sub>5</sub>	+1.6γ		
C-4	70.0 <sub>9</sub>	73.3 <sub>8</sub>	75.9 <sub>6</sub>	72.7 <sub>0</sub>	76.2 <sub>8</sub>	+3.6β	+3.2β	71.4 <sub>9</sub>	74.6 <sub>1</sub>	71.2 <sub>2</sub>	74.5 <sub>0</sub>	+3.3β		
C-5	38.3 <sub>6</sub>	39.4 <sub>4</sub>	40.8 <sub>3</sub>	31.5 <sub>0</sub>	31.5 <sub>0</sub>	0α	+1.6α	37.1 <sub>7</sub>	38.7 <sub>9</sub>	28.7 <sub>0</sub>	30.1 <sub>6</sub>	+1.5α		
C-6	51.6 <sub>9</sub>	51.6 <sub>9</sub>	58.9 <sub>1</sub>	51.5 <sub>6</sub>	59.4 <sub>5</sub>	+7.9β	+5.0β	50.8 <sub>8</sub>	55.8 <sub>3</sub>	50.6 <sub>1</sub>	56.2 <sub>1</sub>	+5.6β		
C-1'	46.2 <sub>9</sub>	46.2 <sub>9</sub>	46.1 <sub>2</sub>	46.4 <sub>9</sub>	46.5 <sub>6</sub>			43.4 <sub>9</sub>	43.4 <sub>3</sub>	44.4 <sub>6</sub>	44.5 <sub>6</sub>			
C-Me		12.3 <sub>0</sub>	12.2 <sub>4</sub>	16.2 <sub>9</sub>	16.5 <sub>2</sub> (a) 12.8 <sub>4</sub> (eq)	+0.3δ	-0.1δ	11.8 <sub>7</sub>	11.9 <sub>8</sub>	15.5 <sub>4</sub>	14.5 <sub>5</sub> 12.5 <sub>9</sub>	-1.0δ		
C-q	149.0 <sub>2</sub>	147.4 <sub>6</sub>	145.6 <sub>0</sub>	147.2 <sub>4</sub>	145.4 <sub>9</sub>	-1.8γ	-2.0γ	145.0 <sub>0</sub>	142.9 <sub>6</sub>	144.6 <sub>5</sub>	143.0 <sub>6</sub>	-1.6δ		

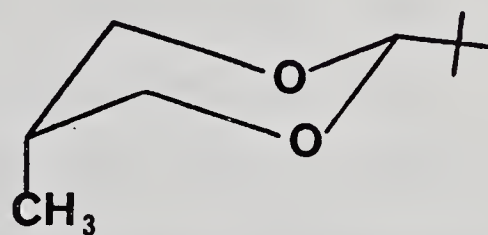
<sup>a</sup> Solvent: CDCl<sub>3</sub>.<sup>b</sup> Δ<sup>b</sup> ppm: Additivity Parameters of equatorial methyl.<sup>c</sup> Reference .<sup>d</sup> Chair conformation, αR, substituent axial, -R, substituent equatorial.



the C-5 position, which effectively compensates for the 'normal'  $\alpha$ -effect. The C-1' carbon resonance was assigned by a proton selective decoupling experiment, the chemical shift is identical to that in the 1,3-dimethyl system ( $11a(\beta)$ ). Selective decoupling of the ring methyls was not possible due to the small differences in their proton chemical shifts (Table III). However, the 16.6<sub>2</sub> ppm and 12.8<sub>4</sub> ppm shifts are assigned to the axial and equatorial methyl carbons, respectively. The high field shift compares favourably with those in the  $\alpha$ -isomer (12.2<sub>4</sub> ppm) and in  $11a(\alpha)$  (12.3<sub>0</sub> ppm)<sup>55</sup>. The low field shift of the axial methyl group is attributed to removal of the hydroxyl group  $\gamma$ -gauche effect which is present in the equatorial methyl substituted compounds. In cis- and trans-2-t-butyl-5-methyl-1,3-dioxanes<sup>92</sup> the identical geometric relationship occurs with the axial C-5' methyl group deshielded (3 ppm) compared to that in the equatorial isomer.



trans-1,3-dioxane



cis-1,3-dioxane

Recently, Eliel and co-workers<sup>34</sup> have described a hyperconjugative-type interaction arising between the free-electron pairs centered on the oxygen atom with the  $C_{\alpha} - C_{\beta}$  bond which is accompanied by a subsequent alternation of the electron density at the  $\gamma$ -anti-periplanar carbon, i.e. equatorial methyl, to explain this effect. An identical explanation can be used in the nitrogen compounds to account for the shielding of the equatorial methyl group ( $11a(\alpha)$  and ( $\gamma$ )) relative to the axial methyl group ( $11a(\beta)$  and  $\gamma$ ).



Two important features arise from the derivation of the additivity effects by comparing the free base and corresponding hydrochloride salt chemical shifts (Table IV). (a) The equatorial methyl  $\beta$ -deshielding effect is attenuated by 2 ppm at the C-6 carbon in the hydrochlorides relative to the free base. Presumably the positive charge on the nitrogen restricts the positive character of the adjacent carbon atom. (b) The  $\gamma$ -effect at C-3 is increased by 2 ppm when the methyl groups are trans orientated in the free base of the  $\gamma$ -isomer compared to the cis-diequatorial methyls of the  $\alpha$ -isomer. It is not clear why an axial substituent at the  $\gamma$ -carbon should increase the  $\gamma$ -effect of the equatorial methyl, other model compounds need to be studied.

Comparison of the ring methyl carbon shifts in compounds  $\underset{\sim}{17}$  (Table II), 11a( $\alpha$ ) and 11a( $\beta$ ) (Table IV) upon introduction of the equatorial methyl gives the gauche-trans and trans-trans  $\delta$  effects for the methyl carbons in compound 11a( $\beta$ ) and 11a( $\alpha$ )/ $\underset{\sim}{17}$ , respectively. The gauche-trans  $\delta$ -effect is small and deshielding (+0.3 ppm) but in the hydrochloride has a shielding value of -1.0 ppm. This value is quite large in comparison to the values reported in the literature<sup>37</sup> (+0.5 ppm). The trans-trans  $\delta$ -effect in both  $\underset{\sim}{17}$  and  $\underset{\sim}{11a(\alpha)}$  is small and shielding, -0.5 and -0.1 ppm, respectively. As expected<sup>43</sup> protonation of the nitrogen atom results in upfield shifts at all piperidine ring carbons (Table II).

The proton chemical shifts for the N-methyl and ring methyl proton resonances in the  $\alpha$ ,  $\beta$  and  $\gamma$  free bases and hydrochlorides are given in Table III. The pmr results for the  $\gamma$ -isomer clearly differentiates the axial and equatorial methyls (assigned by magnitude of the coupling constants compared to  $\alpha$ - and  $\beta$ -isomers). The hydrochlorides of



all three isomers show coupling between the  $\overset{\oplus}{\text{N}}\text{-H}$  and N-methyl protons of approximately 5 Hz.

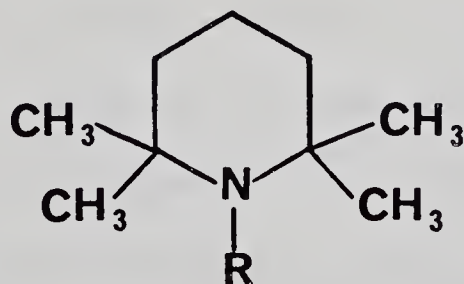
## CONCLUSION

The cmr and pmr spectral evidence thus allow unambiguous assignment of the conformations of the three isomers,  $\alpha$ -,  $\beta$ - and  $\gamma$ -1,3,5-trimethyl-4-phenyl-4-piperidinol.

## B. The Stereochemistry of 1,2,2,6,6-Pentamethyl-4-piperidone and some of its Derivatives

### INTRODUCTION

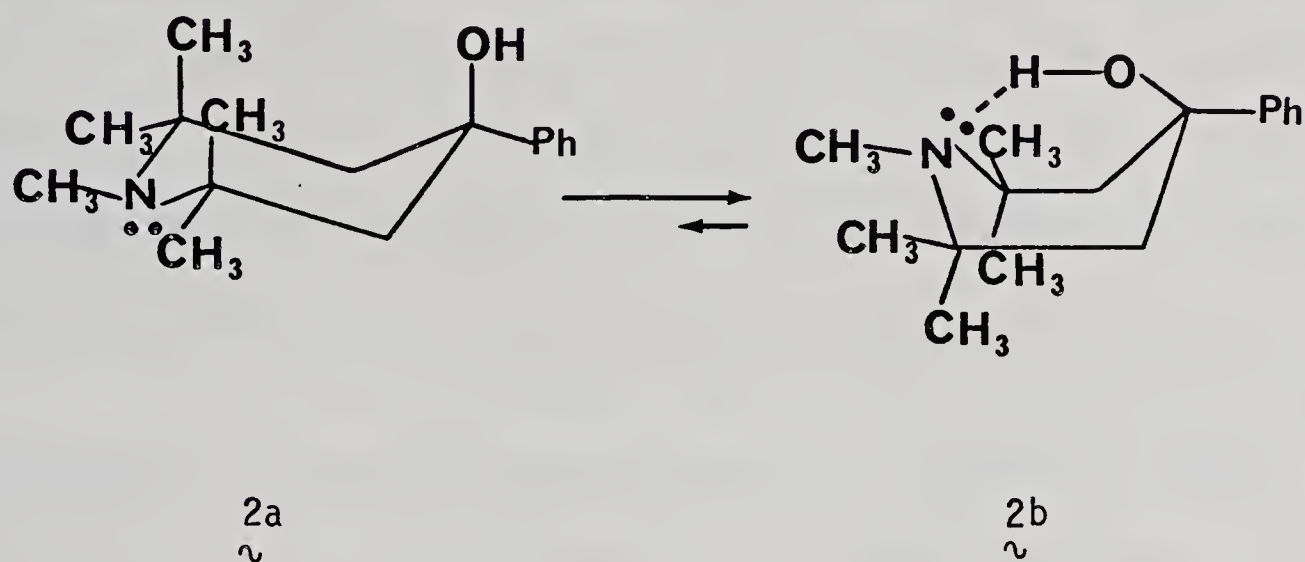
The 2,2,6,6-tetramethylated piperidine skeleton has various pharmacological properties depending on the substituents present on the C-4 carbon position<sup>93</sup>. However, stereostructural-activity relationships have not been reported for these systems. Hence we have studied the 4-oxo and 4-hydroxyl derivatives of 18 and the 4-oxo, 4-hydroxyl and 4-phenyl-4-ol derivatives of 19. The most interesting aspect of the pentamethyl system is the steric congestion about the nitrogen center.



18 R = H;      19 R = CH<sub>3</sub>.



Attempts to N-methylate the 4-oxo derivative of 18 with methyl iodide failed even under refluxing conditions. Steric interactions are increased upon introduction of an axial group at the C-4 position. Infrared studies<sup>10</sup> have shown that the equilibrium of the phenylalcohol (2a) lies to the right (2b), the chair form having extreme steric strain due to the



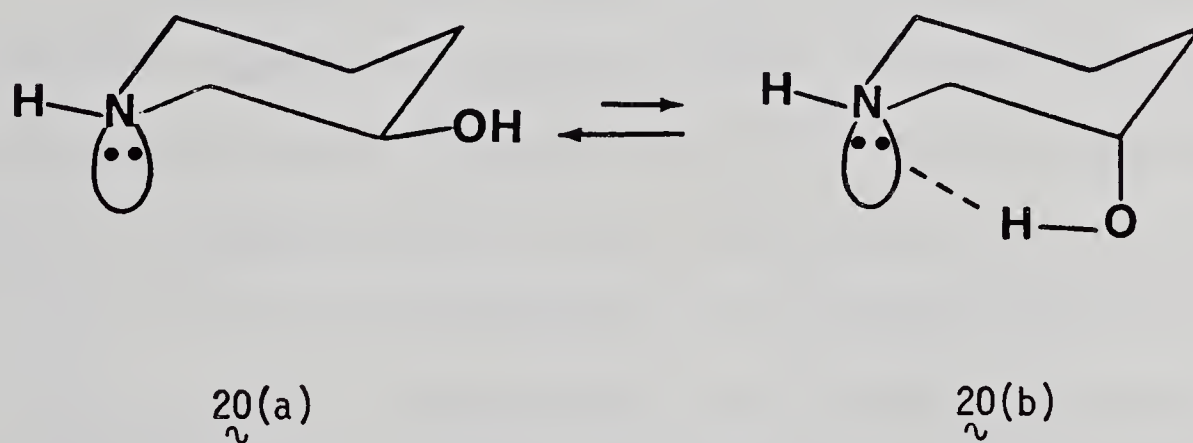
three opposing axial substituents. The attempt to observe the  $-N \cdots H-O$  interaction in the above molecule was studied with an emphasis on the possible breakdown of additivity relationships in the proposed non-chair conformation.

Recent independent cmr studies by Jones<sup>94</sup> and Lippman<sup>95</sup> have shown the equivalence of the methyl groups in 2,2,6,6-tetramethylpiperidine (18). However, owing to different interpretations concerning the use of Grant's additivity parameters<sup>30b</sup>, conflicting views of the molecule's conformation have resulted (vide infra). The similar 3,3,5,5-tetramethylcyclohexanone has been subjected to considerable study using pmr<sup>96</sup> and cmr<sup>97</sup> methods. St. Jacques<sup>96</sup> has provided evidence for the chair conformation of this ketone. However, Stothers'<sup>97</sup> results suggest



distortion in this system from the perfect chair. Similar substitution of methyl groups in the 1,3-dioxanes has been investigated by Kellie and Riddell<sup>26</sup>. These authors suggest that the 2,4-syn-axial interaction of methyl groups in the 2,2,4,4-tetramethyl substituted 1,3-dioxanes cause the molecule to prefer a 'deformed chair' conformation. Other workers have studied pmr line broadening effects in N-sulfinyl, -sulfenyl and -sulfonyl derivatives of 2,2,6,6-tetramethyl-4-piperidone<sup>98</sup>. Even with these large bulky groups it was found that nitrogen atom inversion was as rapid for the N-sulfonyl derivative as for N-H and N-Me tetramethyl-4-piperidones. However, the rate was slowed down sufficiently for the sulfenyl and sulfinyl derivatives to allow axial and equatorial methyl groups to be observed.

3-Piperidinol  $\sim$ 20 has been shown by I.R.<sup>25</sup> to exist in a form which demands intramolecular hydrogen bonding. The hydroxyl group adopts the sterically less favourable axial orientation  $\sim$ 20(b). A pmr



study<sup>99</sup> has been reported and the estimated mole fraction of conformer  $\sim$ 20(a) given as 0.64 when determined in  $\text{CCl}_4$ , corresponding to a conformational free-energy difference of approximately 0.37 kcal/mole for the 3-hydroxyl at  $30^\circ$ . We have attempted to observe this interaction using



carbon-13 nmr in order to establish the contributions made by intramolecular hydrogen bonding to  $^{13}\text{C}$ -shifts.

## RESULTS

The observed carbon-13 chemical shifts for the N-H and N-methyl 2,2,6,6-tetramethylpiperidin-4-oxo  $\underline{24}$  and  $\underline{26}$  and 4-ol derivatives  $\underline{25}$  and  $\underline{27}$  and their corresponding hydrochloride salts along with the supporting data for piperidine, 2-methyl, 2,6-dimethyl and 2,2,6,6-tetramethylpiperidine, ( $\underline{21}$ ,  $\underline{22}$ ,  $\underline{23}$  and  $\underline{18}$ ) are presented in Table V. Table VI summarizes the  $^{13}\text{C}$  chemical shifts for the 1-methyl-( $\underline{10a}$ ), 1,2,6-trimethyl ( $\underline{28}$ ) and 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol ( $\underline{2}$ ), along with a solvent study for the latter. The protonation effects on these compounds are given in Table VII. Table VIII summarizes the  $\alpha$ -,  $\beta$ - and  $\gamma$ -additivity effects arising from introduction of methyl substituents at the C-2 and C-6 positions in a series of piperidines and the C-3 and C-5 positions in cyclohexanone. The effects of solvent variation on the  $^{13}\text{C}$  chemical shift of  $\underline{20}$  are summarized in Table IX.

The condensation of phorone with aqueous methylamine is well known<sup>100,108</sup>. However the product was always isolated as the free base and then characterized. Instead, in a similar reaction we isolated the product as a hydrochloride and after workup obtained two fractions. Extraction of the crude hydrochloride with chloroform gave one fraction, the remaining material being soluble only in water. We denote these extracts  $\text{CHCl}_3 \cdot \text{HCl}$  and  $\text{H}_2\text{O} \cdot \text{HCl}$ , respectively ( $\underline{26a} - \text{CHCl}_3$ ,  $\underline{26a} - \text{H}_2\text{O}$ ). Solvent studies using  $\text{DMSO-d}_6$ ,  $\text{CD}_3\text{OD}$ ,  $\text{CD}_3\text{OH}$ ,  $\text{D}_2\text{O}$  and  $\text{CDCl}_3$  were carried out on the  $\text{CHCl}_3 \cdot \text{HCl}$  extract and  $\text{D}_2\text{O}$  and  $\text{CD}_3\text{OD}$  for the  $\text{H}_2\text{O} \cdot \text{HCl}$  extract. These results are summarized in Table X.

Assignments of the carbon-13 resonances to the appropriate



TABLE V

Carbon-13 Chemical Shifts<sup>a</sup> Of 4-Methylene-, 4-oxo- and -4-ol Derivatives of NH and NCH<sub>3</sub> Piperidines

Carbon Position	18	19	21	22	23	24	24a	25	26	Compound	26a·CHCl <sub>3</sub>	26a·H <sub>2</sub> O	27 <sup>+</sup>	27 <sup>+</sup>	27a
C-2,6	49.7 <sup>c</sup> (49.6 <sub>3</sub> )	53.5 <sup>e</sup>	47.7 <sup>c</sup> (47.7) <sup>b</sup>	53.37 <sup>f</sup> (48.20) <sup>g</sup>	52.8 <sup>c</sup> (52.4) <sup>f</sup>	54.8 <sub>6</sub>	60.0 <sub>0</sub>	52.4 <sub>4</sub>	58.7 <sub>5</sub>	67.0 <sub>6</sub>	57.5 <sub>7</sub>	55.3 <sub>5</sub>	56.4 <sub>8</sub>	66.1 <sub>4</sub>	
C-3,5	38.9 (38.6 <sub>8</sub> )	40.8	27.7 (27.5)	35.9 <sup>g</sup> (27.4 <sub>8</sub> )	34.7 (34.5)	53.7 <sub>8</sub>	49.7 <sub>5</sub>	48.0 <sub>7</sub>	55.7 <sub>2</sub>	52.1 <sub>1</sub>	48.1 <sub>8</sub>	50.1 <sub>2</sub>	50.3 <sub>3</sub>	46.8 <sub>2</sub>	
C-4	18.8 (18.4 <sub>0</sub> )	17.7	25.7 (25.5)	(26.3 <sub>3</sub> )	25.5 (25.4)	210.2 <sub>8</sub>	208.1 <sub>3</sub>	64.4 <sub>1</sub>	209.6 <sub>9</sub>	202.3 <sub>0</sub>	210.7 <sub>2</sub>	63.5 <sub>5</sub>	63.6 <sub>0</sub>	60.5 <sub>3</sub>	
C-1'									28.6 <sub>4</sub>	29.0 <sub>8</sub>	26.8 <sub>2</sub>	28.0 <sub>5</sub>	28.3 <sub>8</sub>	29.4 <sub>0</sub>	
C-2'6'	32.5 (31.6 <sub>7</sub> )	27.3		24.0 <sub>2</sub>	23.5 (23.4)	31.8 <sub>3</sub>	27.5 <sub>8</sub>	28.2 <sub>7</sub> (a) 34.3 (eq)	27.3 <sub>0</sub>	22.6 <sub>0</sub> (a) 28.6 <sub>4</sub> (eq)	23.0 <sub>4</sub>	20.6 <sub>1</sub> (a) 33.3 <sub>4</sub> (eq)	21.0 <sub>4</sub> (a) 33.1 <sub>2</sub> (eq)	21.5 <sub>8</sub> (a) 29.4 <sub>0</sub> (eq)	

<sup>a</sup> Solvents. CDCl<sub>3</sub>: 24, 26, 26a·CHCl<sub>3</sub> and 27<sup>+</sup>.CD<sub>3</sub>OD: 25, 27<sup>+</sup> and 27<sub>a</sub>.D<sub>2</sub>O: 24a and 26a·H<sub>2</sub>O.<sup>b</sup> Values obtained for CDCl<sub>3</sub> solution - J. Leung, Thesis, University of Alberta, 1975.<sup>c</sup> Taken from Reference 94; solvent C<sub>6</sub>D<sub>6</sub>: original data converted using  $\delta_{C_6D_6}^{CD_6} = 128.54$ .<sup>d</sup> Solvent CDCl<sub>3</sub>.<sup>e</sup> Calculated values only.<sup>f</sup> Reference 43; Solvent: Neat.<sup>g</sup> Top value C-2 and C-3, bottom value C-6 and C-5.



TABLE VI

Carbon-13 Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated  
4-phenylpiperidin-4-ols

Carbon Position	Compound Solvent					
	$10\alpha^a$	$28\alpha^a$	$2\alpha$	$2\alpha$	$2\alpha^c$	$2\alpha$
	$\text{CDCl}_3$	$\text{CDCl}_3$	$\text{CDCl}_3$	$\text{CS}_2$	$\text{DMSO}_{d-6}$	$\text{CD}_3\text{OD}$
C-2,6	51.6 <sub>9</sub>	54.8 <sub>6</sub> <sup>b</sup> 47.3 <sub>2</sub>	54.8 <sub>6</sub>	55.3 <sub>1</sub>	55.3 <sub>6</sub>	57.0 <sub>2</sub>
C-3,5	38.3 <sub>6</sub>	43.6 <sub>5</sub> <sup>b</sup> 39.0 <sub>6</sub>	51.8 <sub>9</sub>	51.7 <sub>0</sub>	52.7 <sub>1</sub>	51.4 <sub>6</sub>
C-4	70.0 <sub>9</sub>	73.4 <sub>3</sub>	73.4 <sub>7</sub>	73.2 <sub>2</sub>	73.5 <sub>4</sub>	73.6 <sub>3</sub>
C-2'6'(axial)		13.4 <sub>9</sub>	28.5 <sub>9</sub>	26.0 <sub>2</sub>	23.0 <sub>4</sub>	22.8 <sub>2</sub>
C-2'6'(equat.)		19.8 <sub>6</sub>	29.6 <sub>1</sub>	31.6 <sub>3</sub>	35.5 <sub>6</sub>	32.8 <sub>5</sub>
C-1'	46.2 <sub>9</sub>	46.8 <sub>3</sub>	28.0 <sub>0</sub>	28.4 <sub>4</sub>	29.3 <sub>6</sub>	28.5 <sub>4</sub>
$\text{C}_{\text{q}}$	149.0 <sub>2</sub>	149.3 <sub>5</sub>	148.8 <sub>3</sub>	149.7 <sub>7</sub>	152.7 <sub>3</sub>	150.8 <sub>9</sub>
$\text{C}_{\text{o}}$	128.2 <sub>5</sub>	128.2 <sub>5</sub>	128.1 <sub>2</sub>	128.3 <sub>5</sub>	129.1 <sub>6</sub>	128.7 <sub>7</sub>
$\text{C}_{\text{m}}$	124.7 <sub>4</sub>	124.5 <sub>8</sub>	124.5 <sub>1</sub>	125.0 <sub>6</sub>	126.2 <sub>4</sub>	125.3 <sub>7</sub>
$\text{C}_{\text{p}}$	126.8 <sub>5</sub>	126.7 <sub>9</sub>	126.5 <sub>6</sub>	126.7 <sub>4</sub>	127.4 <sub>3</sub>	127.2 <sub>1</sub>

<sup>a</sup> Reference 55.

<sup>b</sup> Top value being C-2 and C-3 chemical shifts.

<sup>c</sup> Original data converted using  $\delta_{\text{C}}^{\text{DMSO}_{d6}}$  41.17 ppm.



TABLE VII

Protonation Effects on Carbon-13 Chemical Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated  
4-phenylpiperidin-4-ols in Certain Solvents

Carbon Position	Compound and Solvent									
	$10a^a$ CDCl <sub>3</sub>	$10a^a \cdot HCl$ CDCl <sub>3</sub>	$28^a$ CDCl <sub>3</sub>	$28 \cdot HCl^a$ CDCl <sub>3</sub>	$2$ CDCl <sub>3</sub>	$2 \cdot HCl$ CDCl <sub>3</sub>	$2^c$ DMSO-d <sub>6</sub>	$2 \cdot HCl^c$ DMSO-d <sub>6</sub>	$2$ CD <sub>3</sub> OD	$2 \cdot HCl$ CD <sub>3</sub> OD
C-2,6	51.6 <sub>9</sub>	50.6 <sub>1</sub>	54.8 <sub>6</sub> 47.3 <sub>2</sub>	58.2 <sub>2</sub> 51.0 <sub>4</sub>	54.8 <sub>6</sub>	63.9 <sub>8</sub>	55.3 <sub>6</sub>	64.7 <sub>5</sub>	57.0 <sub>2</sub>	65.7 <sub>1</sub>
C-3,5	38.3 <sub>6</sub>	35.0 <sub>1</sub>	43.6 <sub>5</sub> 39.0 <sub>6</sub>	44.4 <sub>6</sub> 40.4 <sub>1</sub>	51.8 <sub>9</sub>	47.8 <sub>0</sub>	52.7 <sub>1</sub>	48.8 <sub>3</sub>	51.4 <sub>6</sub>	49.3 <sub>1</sub>
C-4	70.0 <sub>9</sub>	67.9 <sub>8</sub>	73.4 <sub>3</sub>	71.3 <sub>8</sub>	73.4 <sub>7</sub>	72.3 <sub>4</sub>	73.5 <sub>4</sub>	72.7 <sub>3</sub>	73.6 <sub>3</sub>	72.5 <sub>0</sub>
C2'6' (ax.)			13.4 <sub>9</sub>	13.7 <sub>0</sub>	28.5 <sub>9</sub>	22.7 <sub>6</sub>	23.0 <sub>4</sub>	23.5 <sub>3</sub>	22.8 <sub>2</sub>	22.5 <sub>4</sub>
C2'6' (eq.)			19.8 <sub>6</sub>	17.1 <sub>6</sub>	29.6 <sub>1</sub>	30.1 <sub>0</sub>	35.5 <sub>6</sub>	30.9 <sub>2</sub>	32.8 <sub>5</sub>	30.5 <sub>9</sub>
C-1'	46.2 <sub>9</sub>	43.1 <sub>1</sub>	46.8 <sub>3</sub>	37.8 <sub>8</sub>	28.0 <sub>0</sub>	28.1 <sub>6</sub>	29.3 <sub>6</sub>	29.6 <sub>8</sub>	28.5 <sub>4</sub>	29.6 <sub>2</sub>
C-q	149.0 <sub>2</sub>	146.3 <sub>2</sub>	149.3 <sub>5</sub>	147.4 <sub>6</sub>	148.8 <sub>3</sub>	147.9 <sub>2</sub>	152.7 <sub>3</sub>	150.8 <sub>5</sub>	150.8 <sub>9</sub>	149.8 <sub>9</sub>
C-o	128.2 <sub>5</sub>	128.0 <sub>3</sub>	128.2 <sub>5</sub>	128.2 <sub>5</sub>	128.1 <sub>2</sub>	128.3 <sub>9</sub>	129.1 <sub>6</sub>	129.4 <sub>3</sub>	128.7 <sub>7</sub>	129.3 <sub>1</sub>
C-m	124.7 <sub>4</sub>	124.4 <sub>7</sub>	124.5 <sub>8</sub>	124.9 <sub>1</sub>	124.5 <sub>1</sub>	124.7 <sub>8</sub>	126.2 <sub>4</sub>	126.3 <sub>5</sub>	125.3 <sub>7</sub>	125.6 <sub>7</sub>



TABLE VII (cont'd)

Protonation Effects on Carbon-13 Chemical Shifts of 1-, 1,2,6(trans)- and 1,2,2,6,6-Methylated

4-phenylpiperidin-4-ols in Certain Solvents


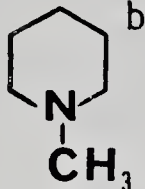
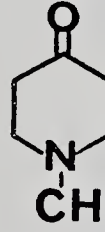
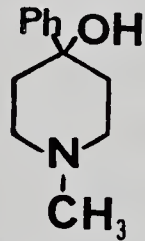
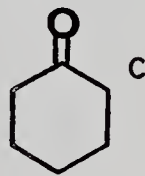
Carbon Position	Compound and Solvent							
	$10a^a$	$10a^a \cdot HCl$	$28^a$	$28 \cdot HCl^a$	$2$	$2 \cdot HCl$	$2^c$	$2 \cdot HCl^c$
C- <u>p</u>	$126.8_5$	$127.0_1$	$126.7_9$	$127.0_6$	$126.5_6$	$127.2_1$	$127.4_3$	$128.1_9$
								$128.1_8$

<sup>a</sup> Reference 55.<sup>b</sup> Top value being C-2 and C-3 chemical shifts.<sup>c</sup> Data converted using  $\delta_c^{DMSO-d_6}$  41.17 ppm.



TABLE VIII

Additivity Parameters for Introduction of 2,2,6,6-Tetramethyl  
Substituents To Some Piperidine Derivatives and 3,3,5,5-Tetramethyl  
Substituent to Cyclohexanone

Compound <sup>a</sup>	Additivity Parameter			
	$\alpha$	$\beta$	$\gamma_{C-4}$	$\gamma_{N-Me}$
	+2.0	+11.2	-6.9	
	-3.1	+14.7	-6.2	
	+3.4	+14.8	+2.6	-16.5
	+3.2	+13.5	+3.4	-18.3
	+8.9	+11.9	$\gamma_{C=O}$ +0.5	

<sup>a</sup> Solvent:  $CDCl_3$ .

<sup>b</sup> Chemical Shifts of N-methylpiperidine: C-2,6 56.6<sub>9</sub>, C-2,5 26.1<sub>1</sub>, C-4 23.9<sub>3</sub>, N-Me 46.9<sub>4</sub>, taken from J. Leung, Thesis, University of Alberta, 1975.

<sup>c</sup> Reference 97.



TABLE IX

Solvent<sup>b</sup> Study of 3-Hydroxypiperidine(20) CMR Shifts<sup>a</sup>

Solvent	Carbon Position				
	C-2	C-3	C-4	C-5	C-6
Dioxane	55.4 <sub>4</sub>	66.9 <sub>9</sub>	35.1 <sub>0</sub>	25.8 <sub>8</sub>	47.3 <sub>5</sub>
C <sub>6</sub> H <sub>6</sub>	54.9 <sub>6</sub>	67.1 <sub>5</sub>	34.5 <sub>1</sub>	25.1 <sub>2</sub>	47.0 <sub>3</sub>
CCl <sub>4</sub>	55.2 <sub>3</sub>	67.4 <sub>2</sub>	34.9 <sub>4</sub>	25.7 <sub>7</sub>	47.5 <sub>1</sub>
CH <sub>3</sub> COCH <sub>3</sub>	55.0 <sub>6</sub>	67.5 <sub>3</sub>	34.6 <sub>7</sub>	25.5 <sub>6</sub>	46.9 <sub>2</sub>
CH <sub>3</sub> OH	53.7 <sub>7</sub>	67.6 <sub>4</sub>	33.9 <sub>2</sub>	25.0 <sub>2</sub>	46.3 <sub>3</sub>
CHCl <sub>3</sub>	55.1 <sub>2</sub>	67.9 <sub>0</sub>	34.7 <sub>3</sub>	25.6 <sub>1</sub>	47.6 <sub>2</sub>
Pyridine	55.7 <sub>7</sub>	67.9 <sub>0</sub>	35.3 <sub>2</sub>	26.1 <sub>0</sub>	47.3 <sub>0</sub>
CH <sub>3</sub> SOCH <sub>3</sub>	55.9 <sub>8</sub>	68.2 <sub>8</sub>	35.8 <sub>1</sub>	26.8 <sub>0</sub>	47.5 <sub>7</sub>
H <sub>2</sub> O	53.1 <sub>2</sub>	68.6 <sub>1</sub>	33.8 <sub>6</sub>	25.2 <sub>9</sub>	46.1 <sub>6</sub>
Average	54.9 <sub>3</sub>	67.7 <sub>1</sub>	34.7 <sub>6</sub>	25.6 <sub>8</sub>	47.4 <sub>8</sub>

<sup>a</sup> External lock C<sub>6</sub>D<sub>6</sub> used as reference; original data converted using  $\delta_c^{C_6D_6} = 128.5_4$ .

<sup>b</sup> 1 molal, sol'n temp. 25°.



TABLE X

Carbon-13 Chemical Shifts of  $\text{CHCl}_3 \cdot \text{HCl}$  and  $\text{H}_2\text{O} \cdot \text{HCl}$  In Various Solvents<sup>a</sup>

Compound and Carbon Position						
$\text{CHCl}_3 \cdot \text{HCl}$						
Solvent	C-1'	C-2',6'(ax.)	C-2',6'(eq.)	C-2,6	C-3,5	C-4
$\text{CDCl}_3$	29.0 <sub>8</sub>	22.6 <sub>0</sub>	28.6 <sub>4</sub>	67.0 <sub>6</sub>	52.1 <sub>1</sub>	202.3 <sub>0</sub>
$\text{CD}_3\text{OD}$	30.3 <sub>7</sub>	22.4 <sub>9</sub>	29.1 <sub>3</sub>	68.8 <sub>3</sub>	53.0 <sub>8</sub>	203.3 <sub>8</sub>
$\text{CD}_3\text{CN}$	30.2 <sub>6</sub>	23.3 <sub>5</sub>	29.1 <sub>8</sub>	68.2 <sub>9</sub>	52.4 <sub>5</sub>	204.4 <sub>5</sub>
$\text{DMSO}_{\text{d}6}^{\text{b}}$	30.3 <sub>8</sub>	23.4 <sub>8</sub>	29.3 <sub>0</sub>	67.9 <sub>8</sub>	53.0 <sub>9</sub>	205.0 <sub>6</sub>
$\text{D}_2\text{O}^{\text{c}}$	29.9 <sub>5</sub>	Broad	Broad	67.4 <sub>0</sub>	51.8 <sub>5</sub>	206.9 <sub>5</sub>
$\text{H}_2\text{O} \cdot \text{HCl}$						
$\text{CD}_3\text{OD}$	27.4 <sub>6</sub>	23.7 <sub>9</sub>	23.7 <sub>9</sub>	58.5 <sub>3</sub>	49.2 <sub>5</sub>	209.9 <sub>6</sub>
$\text{D}_2\text{O}^{\text{c}}$	26.8 <sub>2</sub>	23.0 <sub>4</sub>	23.0 <sub>4</sub>	57.5 <sub>7</sub>	48.1 <sub>8</sub>	210.7 <sub>2</sub>

<sup>a</sup> Solution approx. 250 mg/2 mls of solvent.

<sup>b</sup> Original data converted using  $\delta_{\text{C}}^{\text{DMSO}_{\text{d}6}} = 41.17$  ppm.

<sup>c</sup> Original data converted using  $\delta_{\text{C}}^{\text{Dioxane}} = 66.7_4$  ppm.



carbon position in the compounds studied were made using conventional techniques as discussed in Chapter One.

## DISCUSSION

### 1. General Additivity Effects in the 2,2,6,6-Tetramethyl System

The chemical shifts for piperidine,  $\underset{\sim}{21}$  and 2,6-dimethyl-piperidine  $\underset{\sim}{23}$ , have been reported in the literature<sup>43,94</sup>. Although the determinations were for neat liquids and a solution in  $C_6D_6$ , the shifts agree to within 0.5 ppm. Hence solvent effects must be considered minimal. Comparison of  $\underset{\sim}{21}$  with the 2-methyl derivative  $\underset{\sim}{22}$  gives additivity parameters for an equatorial methyl,  $\alpha + 5.7$ ,  $\beta + 8.5$  and  $\gamma + 0.7$  ppm. Analogous parameters derived for 2,6-dimethylpiperidine  $\underset{\sim}{23}$  are  $\alpha + 4.7$ ,  $\beta + 1.5$  and  $\gamma + 0.7$  ppm. The noticeable decrease in the  $\beta$ -effect arises from the fact that the diaxial conformer will only be present to a small extent in  $\underset{\sim}{23}$  due to severe 1,3-diaxial interactions, hence chair to chair interconversion will not be as important for  $\underset{\sim}{23}$  as in  $\underset{\sim}{21}$  and  $\underset{\sim}{22}$ . The value 23.4 ppm can be taken as a typical (C-2'6') equatorial ring methyl shift. On further methyl substitution at the 2,6-position, as in  $\underset{\sim}{18}$ , the axial and equatorial methyls become equivalent and only one methyl resonance is observed at 31.6<sub>7</sub> ppm (CDCl<sub>3</sub>). It is expected that the chair to chair interconversion will be rapid since in each chair there exists the same syn-diaxial interactions.

The carbon chemical shifts of  $\underset{\sim}{19}$  were not obtained directly but rather calculated from the additivity effects obtained by comparing  $\underset{\sim}{24}$  and  $\underset{\sim}{26}$ ; and  $\underset{\sim}{25}$  and  $\underset{\sim}{27}$ , (replacing N-H by N-Me) the average additivity parameters are  $\alpha + 3.9$ ,  $\beta + 2.1$ ,  $\gamma_{C-4} - 0.7$  and  $\gamma_{C-Me} - 4.4$  ppm.



Applying these parameters to  $\underset{\sim}{18}$  enables calculation of the chemical shifts in  $\underset{\sim}{19}$ . Carbonyl group substituent parameters were derived by comparing  $\underset{\sim}{18}$  and  $\underset{\sim}{24}$ . ( $\alpha + 15.1$ ,  $\beta + 5.2$  and  $\gamma_{C-Me} + 0.2$  ppm). Consideration of the carbonyl effect on the calculated shifts in  $\underset{\sim}{19}$  provides data for  $\underset{\sim}{26}$ . The calculated and observed shifts in  $\underset{\sim}{26}$  are in excellent agreement [C-2,6 (0.0), C-3,5 (0.2) and C-2',6' (0.2 ppm)].

Table VIII gives the additivity effects arising from introduction of gem-dimethyl substituents in a series of piperidine ring systems and cyclohexanone. The  $\beta$ -effect remains constant in all of the compounds while the  $\alpha$ -effect is greatly attenuated upon introduction of an electronegative nitrogen (compare the substitution of phosphorus, Chapter Four). For the N-methyl and N-H piperidines the  $\gamma$ -effect is shielding, while substitution at the C-4 position by a carbonyl or phenylalcohol group causes a deshielding  $\gamma$ -effect. Introduction of carbonyl for methylene at C-4 removes the readily polarizable C-H bond that is attributable to the shielding  $\gamma$ -effect. Deshielding in the phenylalcohol derivative is due to a conformational change from a chair ( $\underset{\sim}{10a}$ ) to a non-chair in the pentamethyl derivative (2). (vide-infra) A similar deshielding was reported<sup>55</sup> for comparison of  $\underset{\sim}{28}$  and  $\underset{\sim}{10a}$  where introduction of an axial C-2' methyl deshields C-4 (+3.3 ppm). The  $\alpha$ -effect in the tetramethyl substituted systems is deshielding except in the N-methylpiperidine (-3.1 ppm). This shielding effect cannot be explained at this time.

## 2. Specific Conformational Effects

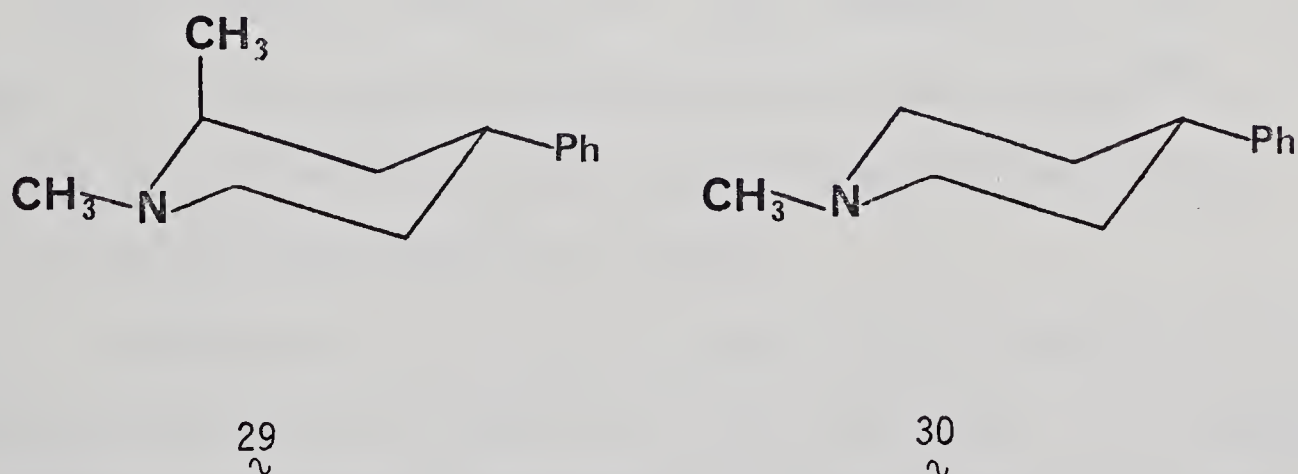
### a. 2,2,6,6-Tetramethylpiperidine Derivatives

As mentioned earlier additivity parameters derived by



Dalling and Grant<sup>30b</sup> have been used to predict the carbon-13 chemical shifts in  $\underset{\sim}{18}$ . However, the conformation of this molecule is still in doubt. Jones et al.<sup>94</sup> suggests a twist structure based on the calculated and observed chemical shift discrepancies (shown in parenthesis), C-2,6 (10.0 ppm), C-3,5 (5.8 ppm) and C-4 (5.4 ppm), while Stothers<sup>102</sup> using Lippmaa's<sup>95</sup> results reports that similar shieldings to those in the methylcyclohexanes operate. From this statement Lippmaa's results might be interpreted in terms of a chair conformation undergoing rapid chair to chair interconversion. The discrepancies quoted by Stothers, C-2,6 (0.2 ppm), C-3,5 (2.5 ppm) and C-4 (3.7 ppm) appear to be significant. It has been reported by Jones<sup>43</sup> that the N-methylpiperidines warrant a different set of additivity parameters from those of the methylcyclohexanes.

We have derived the C-2'6' axial methyl parameter from the reported<sup>103</sup> chemical shifts of  $\underset{\sim}{29}$  and  $\underset{\sim}{30}$  and calculated shieldings for



$\underset{\sim}{18}$  based on the values for  $\underset{\sim}{23}$ . The calculated chemical shifts of  $\underset{\sim}{18}$ , together with the discrepancies (shown in parentheses) from the observed shifts, are C-2,6, 42.3 (7.3), C-3,5, 37.7 (1.0) and C-4, 20.1 ppm (1.7 ppm), respectively. Although these values are in better agreement



than those derived by Jones<sup>94</sup> the large discrepancy for C-2,6 must be considered indicative of distortion in this molecule from a perfect chair. Our interpretation thus supports the skew-boat structure.

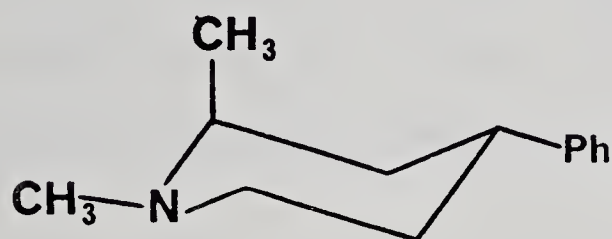
The methyl resonances for the the tetramethyl piperidine 18 absorb 9.0 ppm ( $C_6D_6$  data) downfield compared to those in the dimethyl analog 23. This shift difference is identical to that observed between the 3,5 and 3,3,5,5 methylated cyclohexanones<sup>97</sup>. This value is attributed to the  $\beta$ -effect of the axial methyl upon the equatorial methyl groups and a deshielding syn-axial  $\delta$ -effect for the axial methyls. A concomitant  $\gamma$ -shielding effect of -6.6 ppm occurs at the C-4 position in 23 upon introduction of the axial methyls.

Introduction of a carbonyl group at C-4 in 18 has no effect on the ring interconversion and the methyl resonances remain equivalent. The  $\alpha$ -carbonyl substituent effect is +15.1 ppm in agreement with the value +14.7 ppm reported by Jones and Hassan<sup>43</sup>. The solid state conformation of this piperidone (24) has been described as a distorted chair. However, similar evidence for a chair conformation in the analogous 3,3,5,5-tetramethyl cyclohexanones has been reported<sup>104</sup>. Clearly the solid-state X-ray crystallographic data and the solution studies for these systems cannot be compared.

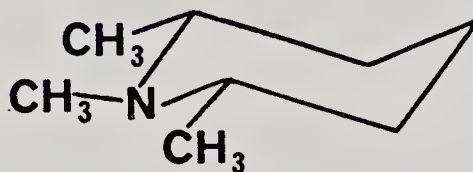
Introduction of an hydroxyl group at the C-4 position as in 25 inhibits interconversion between equivalent conformers. The hydroxyl group prefers the equatorial configuration to avoid the steric interaction with the axial C-2'6' methyl carbons. The additivity parameters for introduction of the equatorial hydroxyl, 25, are in agreement with those for the analogous N-methyl-4-piperidinol<sup>94</sup> ( $\alpha$  + 42.6,  $\beta$  + 8.9 and  $\gamma$  - 2.7 ppm) which is established as preferring the chair conformation.



Hence a similar chair conformation is suggested for  $\underset{\sim}{25}$ . The axial and equatorial methyl carbon atoms in  $\underset{\sim}{25}$  are assigned to the resonances at 28.2<sub>7</sub> and 34.3<sub>1</sub> ppm, respectively. The assignment of the upfield resonance to the axial methyl follows from protonation of 1,2,2,6,6-pentamethyl-4-piperidinol  $\underset{\sim}{27}$ , in which introduction of an axial proton would produce a  $\gamma$ -gauche interaction at the equatorial methyl carbon and hence shielding (-3.7 ppm). The N-H proton and axial methyl are anti to each other and consequently little or no effect is expected at the methyl carbon (+0.5 ppm). Analogous effects are observed in 1,2,6-trimethyl-4-phenyl-piperidin-4-ol ( $\underset{\sim}{28}$ )<sup>55</sup>, trans-1,2-dimethyl-4-phenyl-piperidine ( $\underset{\sim}{29}$ )<sup>103</sup> and 1,2,6-trimethylpiperidine ( $\underset{\sim}{31}$ )<sup>55</sup>.



$\underset{\sim}{29}$



$\underset{\sim}{31}$

It has been postulated<sup>44</sup> that the protonation effect may have some stereospecific nature, the protonation-induced shifts of the  $\gamma$ -carbon atoms falling in the order  $\theta = 0^\circ(\text{cis}) > \theta = 180^\circ(\text{trans}) > \theta = 60^\circ > \theta = 120^\circ$ . However, from the results cited above the order for  $\theta = 180^\circ$ ,  $\theta = 60^\circ$  should be reversed,  $\theta = 60^\circ > \theta = 180^\circ$ . The present results are more consistent with the change in charge density obtained by the

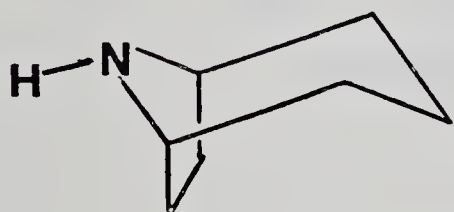


pseudo-atom approach, i.e.  $\theta = 0^\circ(\text{cis}) > \theta = 60^\circ > \theta = 180^\circ(\text{trans}) > \theta = 120^\circ$  (Figure 4).

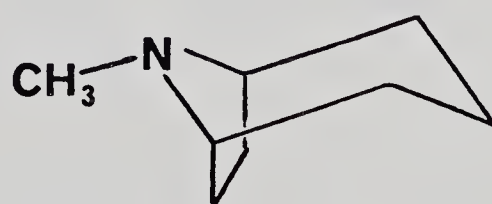
b. 1,2,2,6,6-Pentamethylpiperidine and -4-Piperidinol

The calculated shifts of the piperidine  $\underset{\sim}{19}$  have been described earlier along with the implications caused by steric congestion around the nitrogen atom. The additivity parameters, for introduction of an hydroxyl group obtained by comparing  $\underset{\sim}{19}$  and  $\underset{\sim}{27}$  ( $\alpha$ , +45.9,  $\beta$ , +9.3 and  $\gamma$ , -1.8 ppm) are similar to those reported by Roberts<sup>105a</sup> ( $\alpha$ , +43.2,  $\beta$ , +8.0 and  $\gamma$  -1.1 ppm) for an equatorial hydroxyl group. The equatorial orientation of the hydroxyl group in  $\underset{\sim}{27}$  is thus established.

Comparison of  $\underset{\sim}{25}$  and  $\underset{\sim}{27}$  (changing N-H for N-Me) shows that introduction of an N-methyl group has a large shielding effect (-7.7 ppm) on the axial methyls and only a small shielding effect (-1.0 ppm) on the equatorial methyl carbons. The closest analogy for the former shift is that in the tropane structures  $\underset{\sim}{32}$  and  $\underset{\sim}{33}$ <sup>106</sup>. The C-6,7 carbons



$\underset{\sim}{32}$



$\underset{\sim}{33}$

are axial and are shielded (-3.4 ppm) upon introduction of the N-methyl substituent. Thus, the shielding value (-7.7 ppm) seems exceptionally large. A valid comparison of the equatorial methyl shielding can be



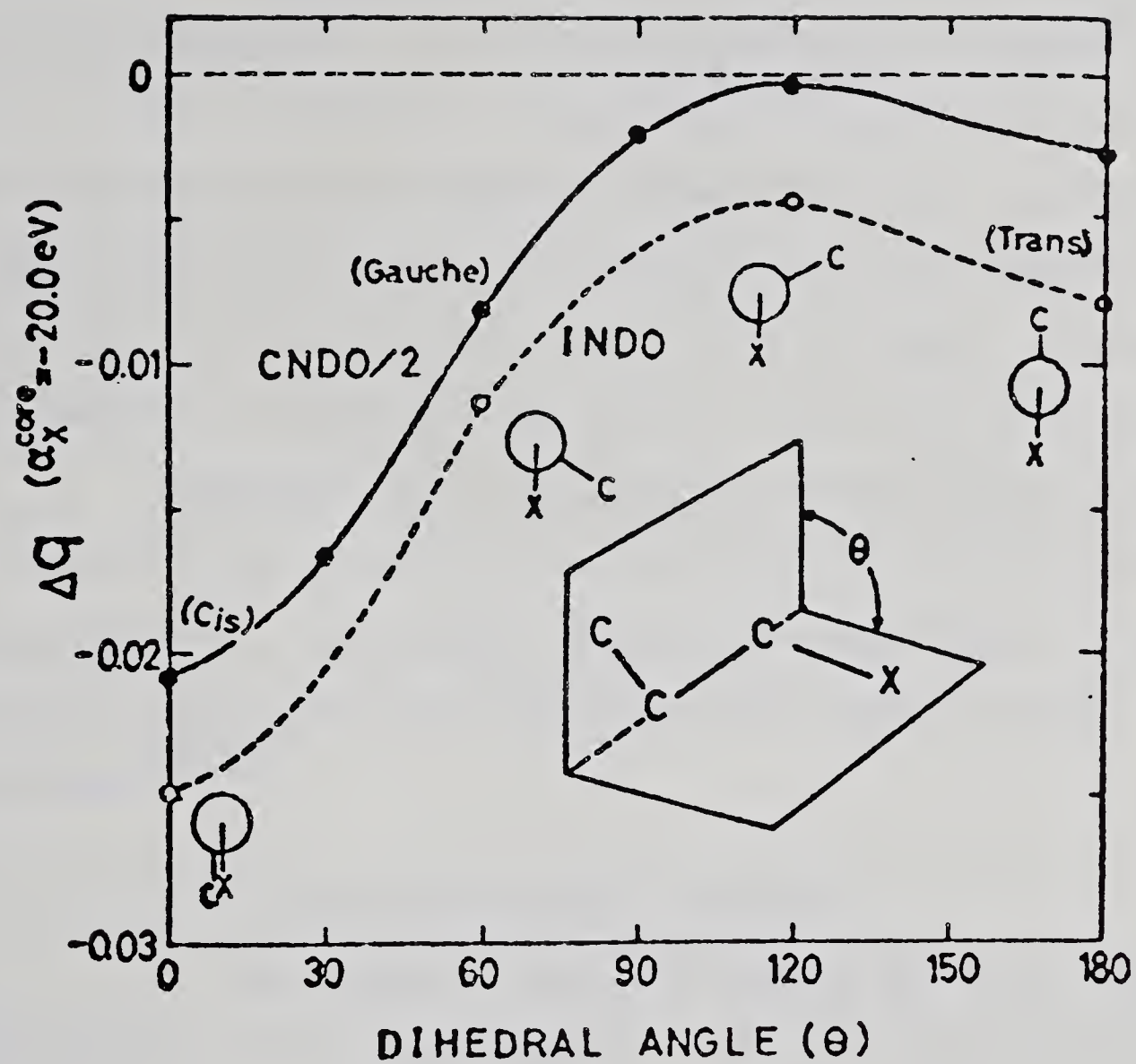


FIGURE 4:  $\Delta q_{\gamma}$  Varying with Dihedral Angle  $\theta$ .<sup>44</sup>



made between 2,6-di and 1,2,6-trimethylpiperidines. Here the equatorial methyls C-2'6' are shielded by 1.5 ppm. In 2- and 2,6-methylpiperidines and their N-methyl derivatives it has been reported<sup>43</sup> that the N-methyl group causes an upfield shift at the ring methyl groups of -2.6 ppm. Similar effects have been established in analogous 1,3-dioxanes<sup>92</sup> and methylcyclohexanes<sup>30b</sup>. The origin of these shifts is thought<sup>43</sup> to be due to steric interactions, the magnitude of the effect being dependent on interatomic distance between the interacting sites. It, therefore, seems likely that the large upfield shift of the axial methyl groups in  $\underline{27}$  is due to ring distortion in which the axial methyl and N-methyl distances are pronounceably shorter than in the perfect chair structure.

Protonation of  $\underline{27}$  causes familiar upfield shifts for the ring carbons with the exception of the substituted C-2,6 positions (deshielded as predicted<sup>43</sup>). The N-methyl carbon is also deshielded (+1.0 ppm) whereas in other piperidine derivatives this carbon is usually shielded<sup>43,55,56</sup>.

#### c. 1,2,2,6,6-Pentamethyl-4-piperidone

The results for the title compound  $\underline{26}$  and its hydrochloride salt require more detailed discussion. The free base and its N-H precursor are freely inverting systems as indicated by the observation of only one methyl resonance in both the pmr and cmr spectra. However, protonation restricts the conformational interconversion and separate carbon resonances are observed for the axial and equatorial methyl groups, 22.6<sub>0</sub> ppm and 28.6<sub>4</sub> ppm, respectively. The shifts are assigned by comparison with the analogous carbon shifts in the 4-piperidinol derivative ( $\underline{27a}$ ) (21.5<sub>8</sub> and 29.4<sub>0</sub> ppm). A second hydrochloride (aqueous extract) ( $\underline{26a} \cdot \text{H}_2\text{O}$ ) derivative was isolated for the 4-piperidone in which



the ring methyls were equivalent (23.0<sub>4</sub> ppm).

The pmr of the aqueous extract hydrochloride exhibited three resonances at 1.3<sub>7</sub>, 2.5<sub>5</sub> and 2.6<sub>1</sub> ppm. Intergration of these regions showed a 12 to 7 proton ratio. Hence, the upfield region was tentatively assigned to the equivalent methyl groups and the lower resonances to the N-methyl and methylene protons, respectively. The pmr of the chloroform extract gave an AB pattern for the methylene protons with  $\nu_A = 2.4$  and  $\nu_B = 3.7$  ppm,  $J_{AB} = 6.5$  Hz. The ring methyls absorbed at 1.3<sub>6</sub> and 1.8<sub>0</sub> ppm, the N-methyl resonance occurred as a doublet  $J_{HH} = 4$  Hz, coupled to the N-H proton and centered at 2.8<sub>7</sub> ppm, the N-H proton resonates at 12.3 ppm. Decoupling at the N-H resonance frequency collapsed the N-methyl doublet to a singlet. Similar N-methyl coupled resonances were observed in the hydrochloride salts of 1,3,5-trimethyl-4-piperidone (17) and of the three 4-phenylalcohol isomers,  $\alpha$ ,  $\beta$  and  $\gamma$ .

The chloroform extract is also soluble in water and its pmr spectrum determined in D<sub>2</sub>O gave only two resonances at 2.8<sub>2</sub> and 1.6<sub>2</sub> ppm. These absorptions fall in the center of the N-methyl doublet and the two methyl resonances for the chloroform solution spectrum (see Figure 5). Further, the chemical shifts for the D<sub>2</sub>O solution of the CHCl<sub>3</sub>·HCl extract are not the same as those in the H<sub>2</sub>O·HCl extract. Spectrum (c) Figure 5, shows the spectrum of the CHCl<sub>3</sub>·HCl extract after being in contact with water for the (b) spectrum, Figure 5, removing water by rotary evaporation and then determining its spectrum in CDCl<sub>3</sub> again. The presence of water clearly results in the N-methyl and ring methyl signals becoming single resonances. The degree of chemical equivalence seems to be dependent on the amount of water present.

The question arises as to the composition of these two extracts.



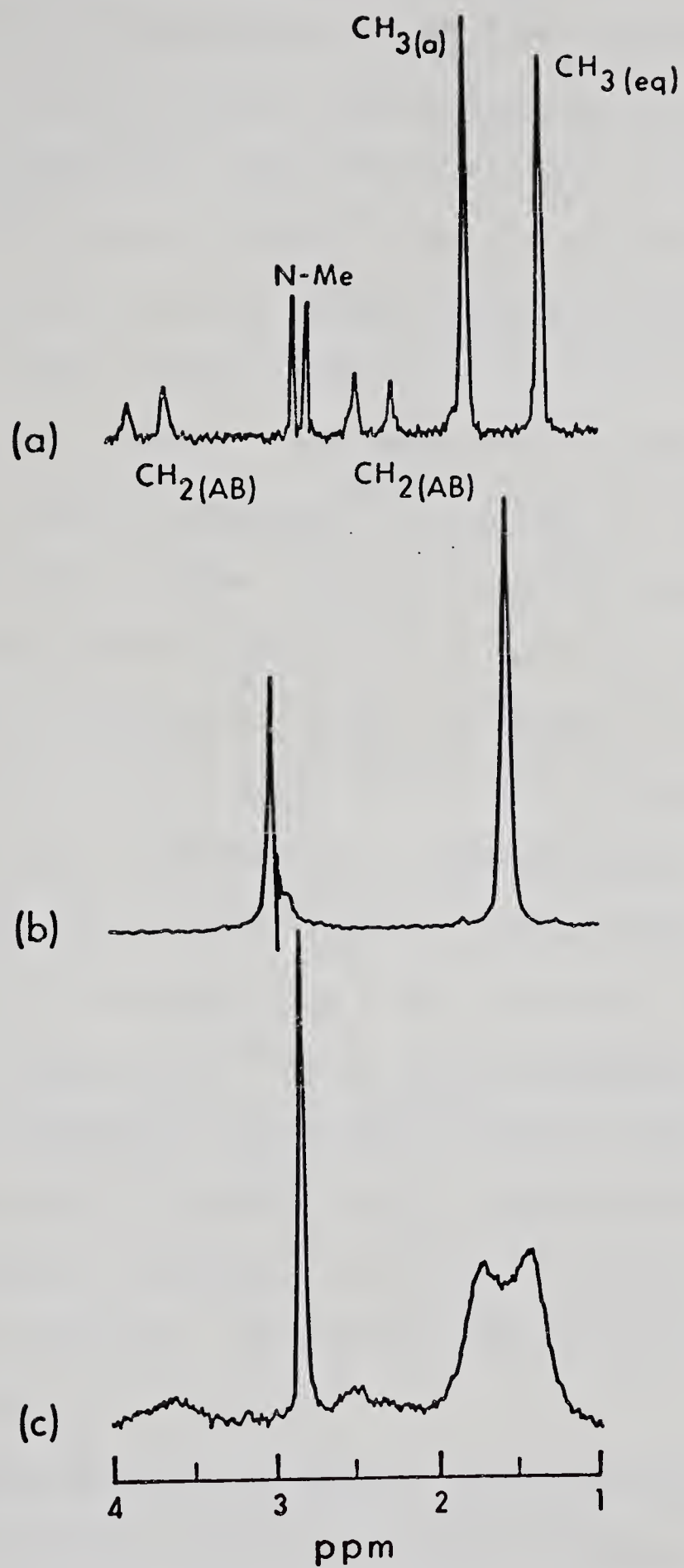


FIGURE 5: Pmr Spectrum of the  $\text{CHCl}_3 \cdot \text{HCl}$  extract in (a)  $\text{CDCl}_3$ , (b)  $\text{D}_2\text{O}$ , and (c)  $\text{CDCl}_3$  after being in contact with  $\text{D}_2\text{O}$ .



Both give the same fragmentation pattern in their mass spectra with parent  $m/e$  169 and mass measurements of 169.1468. Basification of both hydrochlorides gives the identical base as shown by the pmr spectra. The infrared spectrum of the  $\text{CHCl}_3 \cdot \text{HCl}$  (nujol) gave a carbonyl band at  $1720 \text{ cm}^{-1}$  and a  $\overset{\oplus}{\text{N}}\text{-H}$  band at  $2380 \text{ cm}^{-1}$ . The I.R. spectrum of the  $\text{H}_2\text{O} \cdot \text{HCl}$  extract (nujol) had an identical carbonyl stretching absorption, but the  $\overset{\oplus}{\text{N}}\text{-H}$  band was at higher frequency ( $2750 \text{ cm}^{-1}$ ) and additional bands were observed at  $2450$  and  $1590 \text{ cm}^{-1}$ . The latter two absorption bands indicate the presence of a water of hydration<sup>107</sup> as in Figure 6. This explains the concomitant shift to higher frequency of the  $\overset{\oplus}{\text{N}}\text{-H}$  absorption band, the OH band is weakened whereas reduction of the positive charge on nitrogen, consequent upon this interaction renders the  $\overset{\oplus}{\text{N}}\text{H}$  band less polar. A similar observation has been reported<sup>108</sup> for the diastereomeric 1,2-diaryl-4-dimethylamino-3-methylbutan-2-ol hydrochlorides.

Hydrates of the hydrochlorides of similar penta- and tetramethyl compounds have been described in the literature, 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidino<sup>10</sup>  $\cdot \text{HCl}$ , 1,2,2,6,6-pentamethyl-4-piperidino<sup>53</sup>  $\cdot \text{HCl}$  and 2,2,6,6-tetramethyl-4-piperidone<sup>104</sup>  $\cdot \text{HCl}$  all contain water of hydration. The yields of the  $\text{CHCl}_3$  and  $\text{H}_2\text{O}$  hydrochloride extracts is dependent upon reaction conditions, the longer the reaction time, the more  $\text{H}_2\text{O} \cdot \text{HCl}$  extract is obtained. The reaction under anhydrous conditions gave only the  $\text{CHCl}_3$  extract product.

Carbon-13 data help to further characterize the structures of the  $\text{CHCl}_3$  and  $\text{H}_2\text{O}$  extracts and allow the identification of the N-methyl and methylene resonances in the latter. The cmr resonances and chemical shifts are consistent with the structures of the free base and hydrochloride of both extracts. The principle difference between the two



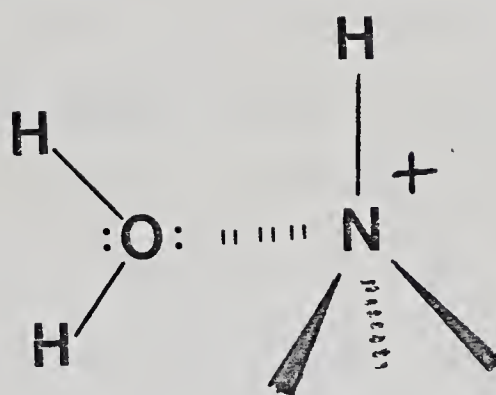


FIGURE 6: Hydrogen bonding between water of hydration and nitrogen.



hydrochlorides is that the aqueous extract gives only a single resonance for the ring methyls. Selective proton decoupling showed that the resonance to high field (2 ppm range) in the pmr spectrum of the free base and hydrochloride of the aqueous extract was due to the N-methyl protons.

A solvent study of the cmr chemical shifts of the  $\text{CHCl}_3$  extract was made in order to observe solvent effects as portrayed in the pmr spectrum. The results are presented in Table X. The chemical shift data is consistent with solvent polarity, the carbonyl resonance moving downfield in the more polar solvent. The only major solvent effect occurred in  $\text{D}_2\text{O}$  where the ring methyl resonances appear as broad signals, indicating an equilibrating situation. Increasing the temperature to  $87^\circ$  coalesced these signals to a singlet at 25.1 ppm. High temperature studies were undertaken with  $\text{DMSO}_{\text{d-6}}$  and  $\text{CD}_3\text{OD}$  as solvents. No change took place in the former. However, in the latter at  $52^\circ$  the ring methyl resonances began to broaden, the other resonances remaining sharp, indicating an approach to an equilibrating situation. It appears that the  $\text{CHCl}_3$  extract in protic media undergoes proton exchange with solvent. This exchange is faster with water than with methanol, water being the smaller molecule. This exchange allows ring interconversion and hence equilivalence of the methyl resonances (25.1 ppm). It should be noted that this shift is to low field compared with that in the aqueous extract (23.0 ppm) but is close to the 27.3 ppm value for the interconverting free base. Further evidence for the proton exchange with the solvent is indicated by the pmr spectra. That is, the N-methyl coupling to the  $\text{NH}$  proton in  $\text{CDCl}_3$  but not in  $\text{D}_2\text{O}$ .

An explanation for the equivalent ring methyls in the aqueous



extract also involves exchange of the  $\text{NH}^{\oplus}$  proton with solvent. The cmr chemical shifts for the  $\text{H}_2\text{O} \cdot \text{HCl}$  extract are all at higher field (except C-4) than the  $\text{CHCl}_3 \cdot \text{HCl}$ , possibly as a result of the water of hydration causing greater steric interactions. The exceptional high field N-methyl resonance of 26.8<sub>2</sub> ppm suggests a contribution from an axial N-methyl conformer. This possibility also follows from the  $\text{NH}^{\oplus}$  exchange argument. For exchange to occur in a finite time the N-methyl group must be at least pseudo-axial in orientation as shown in Figure 7. Interconversion of structure B to A allows for the equivalency of the ring methyl carbons. Structure C is a proposed intermediate, the exchanging of the  $\text{NH}^{\oplus}$  proton from the nitrogen to water occurring from either side.

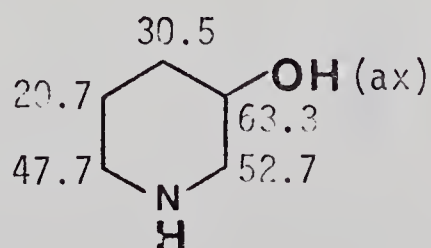
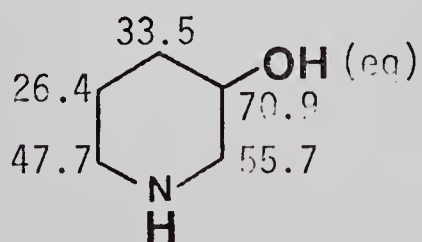
d. 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol

Since a  $\text{N} \cdots \text{HO}$  interaction has been suggested<sup>10</sup> in the title compound a  $^{13}\text{C}$  NMR study on 3-piperidinol, where a similar interaction exists<sup>99</sup>, was undertaken in order to observe the effects on the  $^{13}\text{C}$  chemical shifts.

i. Intra-molecular Hydrogen Bonding - A Model Study

Solutions of 3-piperidinol were made up in dried solvents at 1 molal concentrations. All nmr determinations were carried out at 25°C. In order to avoid inter-molecular effects chemical shifts were measured relative to an external deuterated benzene reference.

The following chemical shifts were calculated using additivity effects for axial and equatorial hydroxyl groups<sup>105</sup> on the piperidine





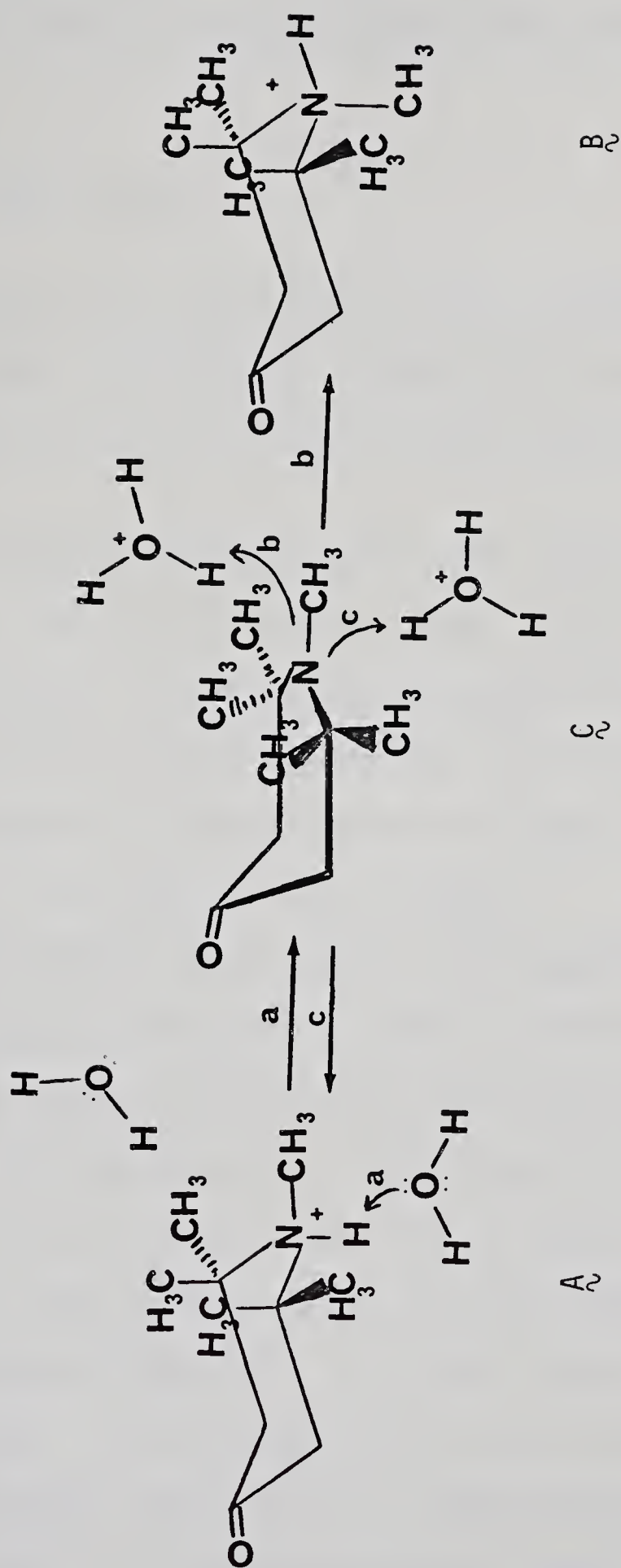


FIGURE 7: Proton exchange between  $\text{N-H}^{\oplus}$  and solvent ( $\text{H}_2\text{O}$ ).



ring. These values and the mole fractions obtained in the pmr studies<sup>99</sup> ( $n_{eq} = 0.64$  for equatorial OH) were used to calculate the expected carbon-13 chemical shifts for an equilibrated solution from the relationship<sup>109</sup>.

$$\delta_{obs} = n_a \delta_a + n_{eq} \delta_{eq}.$$

The following chemical shift values arise C-2:54.6, C-3:68.2, C-4:32.4, C-5:24.3, C-6:47.7 ppm. Discrepancies compared with the observed values ( $CCl_4$ , Table IX) are C-2:+0.6, C-3:-0.8, C-4:+2.5, C-5:+1.5 and C-6:-0.2 ppm.

Table IX lists the solvents used in this study in order of increasing polarity. The only consistent change in chemical shifts occurs at the C-3 carbon. As the polarity increases this carbon shifts to lower field indicating a larger contribution from the equatorial conformer since the equatorial hydroxyl conformer has the C-3 chemical shift at 7.6 ppm to lower field than the axial conformer.

One molal solutions were used for these experiments and hence inter-molecular hydrogen bonding effects cannot be ruled out. Therefore, we also studied 0.2m and 0.1m solutions under the same conditions. Similar chemical shifts were obtained. Infrared spectra were determined for all concentrations of solution ( $CDCl_3$  free of ethanol). The 1 molal solution exhibited a broad hydrogen bonded OH band at  $3280\text{ cm}^{-1}$  and a very small free OH band at  $3600\text{ cm}^{-1}$ . The latter increased in intensity upon dilution to 0.2m. In carbon tetrachloride the 0.1 molal solution exhibited a free-OH band at  $3600\text{ cm}^{-1}$  and a broad band for hydrogen bonded-OH at  $3300\text{ cm}^{-1}$ , the latter being resolved into two bands on dilution to 0.02m, at  $3520\text{ cm}^{-1}$  (OH $\cdots$ N-) and  $3360\text{ cm}^{-1}$  (N-H). From



these data it can be concluded that a significant amount of inter-molecular hydrogen bonding is present at the high concentrations (1m and 0.1m), while at lower concentrations (0.02m) intra-molecular hydrogen bonding is evident. Because of the concentration limitations inherent to cmr measurements the chemical shifts are averaged values and the information obtained from I.R. (0.02m) cannot be duplicated.

We must, therefore, conclude that direct measurement of intra-molecular hydrogen bonding using  $^{13}\text{C}$  nmr measurements is not likely to be valuable unless large conformational changes occur in the molecular system. giving rise to additional features, additivity breakdown, steric  $\gamma$ -gauche effects, etc. These approaches were used in the pentamethylpiperidinol, 2 (vide-infra) and various tropane derivatives (Chapter III).

d. 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol (cont'd)

The conformation of the phenylalcohol, (2) was first investigated by an infrared study. The I.R. of 2 determined in carbon tetrachloride ( $5 \times 10^{-2}$  M) exhibited a sharp band at  $3590\text{ cm}^{-1}$  and a broad band at  $3300\text{ cm}^{-1}$ . The solution used for the  $^{13}\text{C}$  spectral determinations (approximately 1 molal) also showed these absorptions. Thus, it is apparent that the molecule remains in a similar environment in both dilute and concentrated media.

Comparison of cmr data for the free base in a variety of solvents (Table VI) showed a marked solvent dependency especially at the C-2,6 and C-2',6' positions. The analogous pmr results are given in Table XI. These results show that the methylene protons in these solvents are equivalent since a characteristic AB pattern is not observed.



TABLE XI

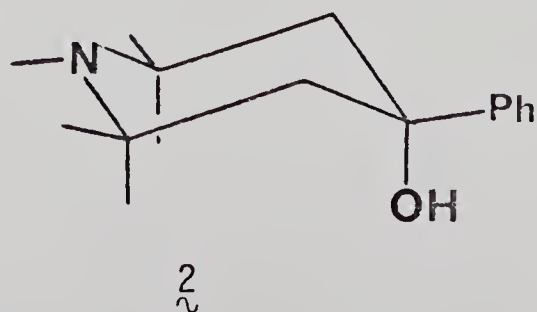
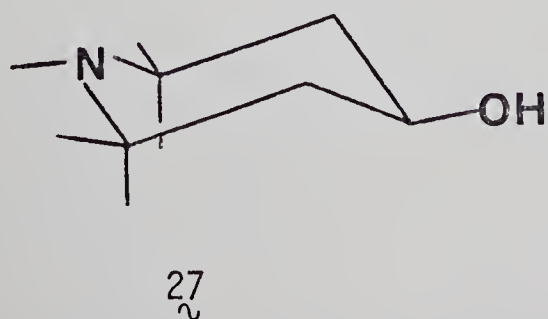
PMR Solvent Study of 1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidino1

	CS <sub>2</sub>	CDCl <sub>3</sub>	CD <sub>3</sub> OD
N-Me	2.2 <sub>8</sub>	2.3 <sub>5</sub>	2.4 <sub>0</sub>
CH <sub>2</sub>	1.8 <sub>2</sub>	1.9 <sub>8</sub>	1.9 <sub>0</sub>
CH <sub>3</sub> (eq)	1.1 <sub>4</sub>	1.2 <sub>1</sub>	1.1 <sub>8</sub>
CH <sub>3</sub> (a)	1.2 <sub>8</sub>	1.3 <sub>5</sub>	1.4 <sub>0</sub>
Phenyl	7.0-7.4	7.3-7.6	7.2-7.6



Instead, a broad signal is observed for these nuclei. The broadest signal was observed in the hydrochloride salt, then the free base in methanol, the sharpest in deuterochloroform. These results confirm that the molecule is in a non-chair conformation with the methylene protons (in the free base) less equivalent in the more polar solvent ( $\text{CD}_3\text{OD}$ ). Intra-molecular hydrogen bonding will favour a 'pseudo'-boat form as the preferred conformation (Figure 8). As the solvent polarity increases, the amount of intramolecular hydrogen bonding decreases and the orientation of the OH bond will be projected as shown in Figure 8b, binding with the solvent at both the hydroxyl and nitrogen ends of the molecule.

The change in the orientation of the hydroxyl group is reflected at the C-2,6 carbon positions, structure b in Figure 8, having a smaller  $\gamma$ -effect at these carbon atoms. The carbon C-2,6 is at lowest field ( $57.0_2$  ppm) in  $\text{CD}_3\text{OD}$  and highest field ( $54.8_6$  ppm) in  $\text{CDCl}_3$ . The 2.1 ppm difference suggests a change in the conformation in these solvents. More dramatic solvent shifts are noticeable at the C-2'6' carbon atoms. However, the carbon-13 chemical shift assignment for the axial and equatorial methyl groups need to be clarified. Thus in compound  $27_{\sim}$  (determined in methanol) the axial and equatorial methyl carbon shifts are  $21.0_4$  ppm and  $33.1_2$  ppm, while the shifts in  $2_{\sim}$  (determined in methanol) are  $22.8_2$  and  $32.8_5$  ppm, respectively. The introduction of the syn-axial hydroxyl in  $2_{\sim}$  is expected to deshield the axial methyls via a  $\delta$ -effect. Compared to  $27_{\sim}$  this equatorial phenyl group will cause





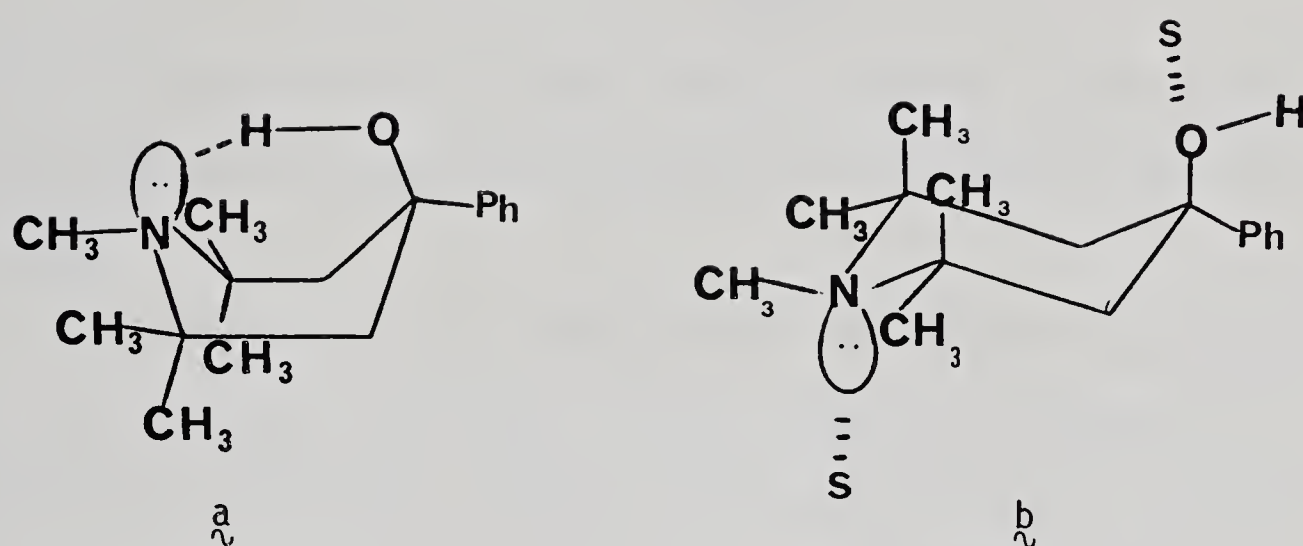
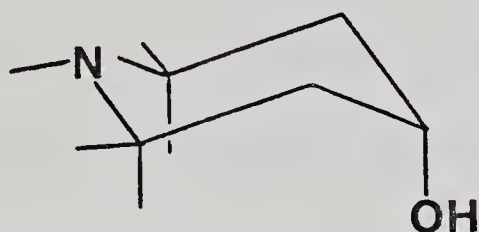


FIGURE 8: Representation of intra-molecular hydrogen bonding in a non-polar solvent (a) and solvation (b) in a polar solvent (S).



very little perturbation of the ring methyls<sup>103</sup>. By using the published<sup>55</sup> equatorial phenyl additivity parameters we calculated the ring carbon chemical shifts for the compound below. Due to the axial hydroxyl group, the axial and equatorial methyl carbons would be expected to resonate at 22.7 and 33.3 ppm, respectively.



Comparison of these shifts with those for the equatorial hydroxyl (27) provides evidence of  $\gamma$ -gauche shielding effect (-6.3 ppm) on the C-2,6 carbon atoms.

The similarity of the carbon shifts for the axial and equatorial methyls of **2** in  $\text{DMSO}_{\text{d-6}}$  and  $\text{CD}_3\text{OD}$  indicates comparable conformations in these solutions (Figure 8b). However, when  $\text{CS}_2$  and  $\text{CDCl}_3$  are employed as solvents a large deshielding of the axial and shielding of the equatorial methyls is observed. The difference between the axial and equatorial methyl shifts are 5 ppm and 1 ppm, respectively, which should be compared with the difference 12 ppm and 10 ppm for solutions in  $\text{DMSO}_{\text{d-6}}$  and  $\text{CD}_3\text{OD}$ , respectively. Taking the methyl shifts of 22.7 and 33.3 ppm as fixed axial and equatorial values (above) an average value of approximately 28.0 ppm can be determined for a freely flipping situation. Thus the 28-29 ppm shift observed for the methyl resonances of **2** in  $\text{CDCl}_3$  solution is close to both the equatorial and average value. An equilibrating system is discounted for by the IR data. Thus, we suggest that in chloroform the four methyl groups must be near equatorial. A feature which can only be achieved in a skew structure. Comparison of the



chemical shifts of the ring methyl carbons of the hydrochlorides of 2<sub>~</sub> determined in  $\text{CDCl}_3$ ,  $\text{DMSO}_{\text{d}-6}$  and  $\text{CD}_3\text{OD}$  show similar values, approximately 22.7 and 30.5 ppm for the axial and equatorial carbons, respectively. Hence the same preferred conformations exist in all of these solvents. The shifts for the free bases then cannot be reconciled on the basis of a solvent effect but rather must be due to a conformational change from a chair in  $\text{CD}_3\text{OD}$  solution to a skew-boat in  $\text{CDCl}_3$ .

### CONCLUSIONS

The cmr study of the 3-piperidinol to detect intra-molecular hydrogen bonding indicated that a strained molecular system must be chosen in order for cmr to detect any conformational change arising from such an interaction. These constraints were present in the 1,2,2,6,6-pentamethyl-4-phenyl-4-piperidinol and a skew-boat conformation is suggested for this structure in deuteriochloroform solution, the molecule undergoing solvent dependent conformational changes in the solvents investigated. In all the pentamethylpiperidines studied non-chair conformations were found. The conformations were assigned as a consequence of protonation effects and in some instances breakdown in additivity parameters. Two fractions were obtained for the hydrochloride derivative of 1,2,2,6,6-pentamethyl-4-piperidone. One contained water of hydration which showed equivalency of the axial and equatorial methyl groups both in its pmr and cmr spectra determined in  $\text{D}_2\text{O}$  (insoluble in chloroform). The other, determined in  $\text{CDCl}_3$  solution, gave separate resonances for these methyl groups and when determined in  $\text{D}_2\text{O}$  evidence for an approach to an equilibrating situation was presented.

The significance of lone-pair deshielding via the anti-periplanar



argument was reinforced by observation of the carbon chemical shift parameters of the  $\alpha$ - and  $\gamma$ -isomers of 1,3,5-trimethyl-4-phenyl-4-piperidinol. The  $\gamma$ -protonation effects observed in the pentamethylpiperidines should encourage further study on the conformational dependence of the  $^{13}\text{C}$  shifts induced by N-protonation.

## EXPERIMENTAL

3-Hydroxypiperidinol, 2,2,6,6-tetramethyl-4-piperidone hydrochloride and 2,2,6,6-tetramethyl-4-piperidinol were obtained from Aldrich Chemical Company. A sample of 2,2,6,6-tetramethylpiperidine was donated by Dr. S. Brown. The remaining compounds were prepared by literature preparations with some modifications. In these cases the boiling points and melting points are uncorrected.

### 1,3,5-Trimethyl-4-phenyl-4-piperidinol ( $\alpha$ -isomer)

The procedure as outlined by Sorokin<sup>89</sup> was followed and this product isolated as a white solid; m.p. 130-131°, m.p. (lit.)<sup>89</sup> 131.5-132° IR (Nujol) 3220  $\text{cm}^{-1}$  (OH str), Mass. Spec. parent m/e 219.

### 1,3,5-Trimethyl-4-phenyl-4-piperidinol ( $\beta$ -isomer)

The procedure as outlined by Sorokin<sup>89</sup> was followed with the modification that the isolation of the title compound was carried out by column chromatography of the mother liquor remaining after the maximum amount of the  $\alpha$ -isomer was removed by crystallization. Chromatography on alumina, eluting with  $\text{CHCl}_3$  followed by methanol. The residual  $\alpha$ -isomer was eluted by the  $\text{CHCl}_3$  and the  $\beta$ -isomer by methanol; m.p. 117-121°, m.p. (lit.)<sup>89</sup> 121-121.5°, IR (Nujol) 3300  $\text{cm}^{-1}$  (OH str), Mass. Spec. parent m/e 219.



1,3,5-Trimethyl-4-phenyl-4-piperidinol ( $\gamma$ -isomer)

The procedure as outlined by Sorokin<sup>89</sup> was followed with the modification that the isolation of the title compound was carried out by column chromatography. After the maximum amount of  $\alpha$ -isomer was isolated through crystallization the residue was subject to column chromatography on alumina eluting with Skelly 'B' benzene 1:3, 4 x 100, then benzene, chloroform 3:1, 4 x 100, 3:1.5, 4 x 100, 1:3, 4 x 100. With the latter solvent system 3 bands separated. The first was eluted and subjected to further column chromatography on alumina, eluting first with Skelly 'B' to remove 'impurities' then with chloroform to isolate the title compound. M.p. 130-135°, m.p. (lit.)<sup>89</sup> 134.5-135°, IR (Nujol) 3300 cm<sup>-1</sup> (OH str). Mass. spec. parent m/e 219.

The hydrochlorides of all three isomers were prepared as outlined by Sorokin<sup>89</sup>.

	<u>M.p. Observed</u>	<u>M.p. Reported</u>
$\alpha$ ·HCl	221-223°	222-222.5°
$\beta$ ·HCl	222-224°	223-225.5°
$\gamma$ ·HCl	240-241°	241-242°

1,2,2,6,6-Pentamethyl-4-piperidone and hydrochlorides

To 69.1 g (0.5 moles) of freshly distilled phorone (Aldrich) 17.5 mls of methanol and 60 mls of 40% aqueous methylamine (excess) was added with stirring, the temperature being kept below 40° by slight cooling. The mixture was heated at 60° for 2 hours and the excess methylamine removed under reduced pressure. The solution was acidified with concentrated HCl, the solvent removed by rotary evaporation and a thick oily residue remained. Addition of acetone afforded brownish crystals, extraction with hot chloroform and removal of solvent gave



brown crystals which after several recrystallizations from acetonitrile gave white prismatic crystals of m.p. 185-187°, I.R. (Nujol) 1720 ( $\text{C}=\text{N}$  str) and  $2380\text{ cm}^{-1}$  ( $\text{NH}$  str). Mass spec. parent m/e 169, [exact mass. 169.1468 (measured), 169.1467 (calculated) correct for  $\text{C}_{10}\text{H}_{19}\text{NO}$ ] Pmr  $\text{CH}_3(\text{s})$  1.3<sub>6</sub> and 1.8<sub>0</sub> ppm. N-methyl(d) 2.8<sub>7</sub> ( $J_{\text{HH}}$  4 Hz).  $\text{CH}_2$ : AB  $\nu_{\text{A}}$  2.4 ppm,  $\nu_{\text{B}}$  3.7 ppm,  $J_{\text{AB}}$  6.5 Hz. Solvent  $\text{CDCl}_3$  ref. TMS. Identified as the hydrochloride of the title compound.

To this residue after extraction with hot chloroform water was added and the solution filtered. The filtrate was removed by rotary evaporation affording white crystals which after several recrystallizations from a mixture of hot acetonitrile and 95% ethanol afforded white crystals of m.p. 169-170°.

I.R. (Nujol 1720 ( $\text{C}=\text{N}$  str) 2750 ( $\text{NH}$  str) and 1590 and  $2450\text{ cm}^{-1}$  ( $\text{H}_2\text{O}$  of hydration).

Mass spec. parent m/e 169, [exact mass. 169.1468 (measured), 169.1467 (calculated) correct for  $\text{C}_{10}\text{H}_{19}\text{NO}$ ] Pmr  $\text{CH}_3(\text{s})$  1.3<sub>7</sub> ppm N-methyl (s) 2.55 ppm  $\text{CH}_2(\text{s})$  2.61 ppm. Solvent  $\text{D}_2\text{O}$  ref. TMS (ext). Identified as the hydrochloride of the title compound.

The free bases from both extracts were generated by dissolving the hydrochloride in a minimum amount of water and adding  $\text{Na}_2\text{CO}_3$  to a pH of 8.5, extraction with chloroform afforded the title compound. B.p. 100° at 15 mm. lit.<sup>101</sup> 122° at 23 mm. Mass spec. m/e 169.

Pmr.  $\text{CH}_3(\text{s})$  1.18 ppm, N-methyl (s) 2.3<sub>5</sub> ppm,  $\text{CH}_2(\text{s})$  2.40 ppm.

#### 1,2,2,6,6-Pentamethyl-4-piperidinol

A mixture of 2.4 g (14 m moles) of 1,2,2,6,6-pentamethyl-4-



piperidone, 1 g of  $\text{LiAlH}_4$  in 150 mls dried THF was stirred under a  $\text{N}_2$  atmosphere and gently refluxed for 2 hours. Addition of water to destroy excess  $\text{LiAlH}_4$ , filtered, extraction with ether, dried over  $\text{MgSO}_4$  and the solvent removed afforded a yellow liquid which crystallized on cooling. Recrystallization from Skelly 'B' gave white needlelike crystals, m.p.  $73-74^\circ$ , 1.5 g (62.5%). Sublimation of product gave no further purification. M.p. (lit.)<sup>53</sup>  $72.8-74^\circ$ . I.R. spectrum (film)  $3270\text{ cm}^{-1}$  (OH str).

1,2,2,6,6-Pentamethyl-4-phenyl-4-piperidinol

A solution of phenyllithium was prepared from 1.3 g (0.18 moles) of Li and 9.4 mls of freshly distilled bromobenzene in 250 mls of ether. 5.1 g (0.03 moles) of 1,2,2,6,6-pentamethyl-4-piperidone in 50 mls of ether was added slowly. After the addition the solution was stirred and kept under an argon atmosphere overnight. On the following day, the solution was refluxed for 1 hour, cooled, 10 mls of benzene was added and the mixture decomposed with 35 mls of water. The ether-benzene layer was separated, the water layer extracted with ether, the extracts combined and dried over  $\text{MgSO}_4$ . The solvent was removed on a rotary evaporator. The product was a thick oil which failed to crystallize. Phenyl impurities were present and were removed by isolating the hydrochloride, extraction into the water then basifying with NaOH 5% to yield the free base devoid of impurities. I.R. ( $\text{CCl}_4$ :  $5 \times 10^{-3}$  M)  $3300$  (H bonded OH) and  $3590\text{ cm}^{-1}$  (free OH). Hydrochloride m.p.  $229-235^\circ$ , lit.<sup>10</sup>  $235-236^\circ$ . Mass spec. m/e 247.

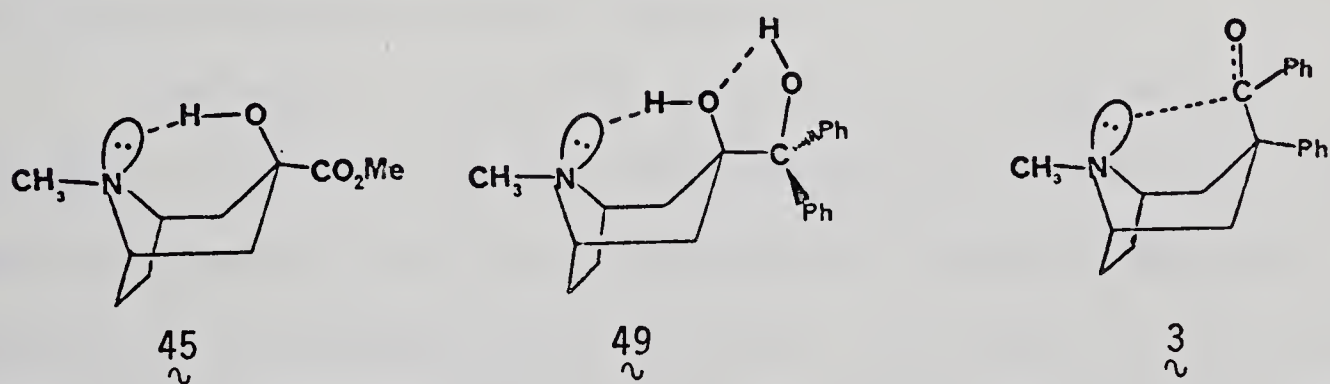


## CHAPTER III

### TROPANES

#### A. INTRODUCTION

There has been much interest in the pmr spectroscopy of tropane ( $\underset{\sim}{33}$ ) due to the relationship of this bicyclic tertiary base to the classical muscarinic antagonist, atropine ( $\underset{\sim}{39}$ ). Many of these studies have been directed towards determining the preference for the boat or chair conformation in tropine ( $\underset{\sim}{38}$ ). A detailed review is available<sup>110</sup>. Most recently, Casy et al.<sup>24</sup> have observed a preference for the boat conformation in the tropane derivatives  $\underset{\sim}{45}$ ,  $\underset{\sim}{49}$  and  $\underset{\sim}{3}$ . This preference is attributed to strong intramolecular hydrogen bonding interactions in these systems, as shown:



Evidence for the preferred boat conformation in  $\underset{\sim}{45}$ ,  $\underset{\sim}{49}$  and  $\underset{\sim}{3}$  is based on the coupling between the 1(5)-H and 2(4)-H protons which is broadened in the boat conformer (compared with the chair) as a consequence of eclipsing of these protons. Independent UV studies on  $\underset{\sim}{3}$  also indicate the  $N \cdots C \cdots O$  interaction<sup>11</sup>.

Carbon-13 studies on tropane derivatives have thus far been



limited<sup>106,111</sup>. A minor controversy exists concerning the assignment of the C-2,4 and C-6,7 methylene carbons. The present study resolves this ambiguity and shows that the highest field resonance of the pair attributable to C-2,4 and C-6,7 must be assigned to C-6,7. Further, the reliability of carbon-13 chemical shifts as an index of preferred conformation especially in non-chair hydrogen bonded structures is tested (for other examples see Chapter II). Carbon-13 nmr provides an unambiguous method for the determination of conformation in these systems.

## B. RESULTS

For the purpose of clarity, we summarize all known carbon-13 data on the tropanes in the Tables to follow. In Table XII data for the tropane derivatives,  $\underline{32}$ ,  $\underline{33}$ ,  $\underline{35}$ ,  $\underline{37}$  previously reported by Wenkert<sup>106</sup> and  $\underline{38}$ ,  $\underline{39a}$  and  $\underline{40}$  reported by Maciel et al.<sup>111</sup> are given. The remaining data was determined in the present work.

Assignment of the carbon resonances was by conventional techniques. Distinction between the methylenes, C-2,4 and C-6,7 is based on comparison with data for protonated 3-tropinone ( $\underline{34a}$ ) and N-methylated 3-tropinone ( $\underline{34b}$ ) derivatives. The chemical shift of the carbons C-2,4 and C-6,7 are 46.5<sub>1</sub> and 24.9<sub>9</sub> ppm in  $\underline{34a}$  and 26.3<sub>7</sub> and 26.3<sub>3</sub> ppm in  $\underline{34b}$ . That is, a larger  $\gamma$ -interaction is apparent at C-2,4 in the N-methyl derivative ( $\underline{34b}$ ) due to the steric compression between the protons at this site and the N-methyl group. Conversely, the resonances at 24.9<sub>9</sub> and 26.3<sub>3</sub> ppm are assigned to C-6,7. In all the tropanes the low field methylene shift is assigned by analogy to C-2,4. Ambiguities remain in the assignment of the quaternary carbon resonances in  $\underline{36}$  and  $\underline{49}$  and the aromatic carbon resonances in  $\underline{3}$  and its



TABLE XII

## The Carbon-13 Chemical Shifts of Tropane Derivatives







Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=O	Ester $\frac{\text{CH}_2}{\text{CH}_3}$	Reference
 32	CDCl <sub>3</sub>		54.7	32.9	29.0	17.2							106
 33	CDCl <sub>3</sub>	40.4	61.2	29.9	25.6	15.9							106
 34	CDCl <sub>3</sub>	38.4 <sub>6</sub>	60.9 <sub>6</sub>	47.6 <sub>9</sub>	27.9 <sub>4</sub>	208.2 <sub>3</sub>							Present
 34a	D <sub>2</sub> O	39.0 <sub>7</sub>	63.2 <sub>9</sub>	46.5 <sub>1</sub>	24.9 <sub>9</sub>	206.9 <sub>5</sub>							Present
 34b	D <sub>2</sub> O	51.4 <sub>7</sub> (a) 45.1 <sub>1</sub> (eq)	69.2 <sub>2</sub>	26.3 <sub>9</sub>	26.3 <sub>3</sub>	208.2 <sub>3</sub>							Present
 35	CDCl <sub>3</sub>	38.6	59.8	39.7	25.3	106.9							106













TABLE XII (cont'd)

## The Carbon-13 Chemical Shifts of Tropane Derivatives

Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=O	Ester CH <sub>2</sub> /CH <sub>3</sub>	Reference
39a 	D <sub>2</sub> O	39.2 <sub>2</sub>	62.3 <sub>1</sub>	34.4 <sub>6</sub>	23.7 <sub>3</sub>	66.5 <sub>0</sub>							Present
39a 	a	39.5 <sub>7</sub>	63.0 <sub>3</sub>	24.0 <sub>3</sub>	35.2 <sub>6</sub>	66.4 <sub>3</sub>							111
40 	a	53.4 <sub>2</sub>	53.7 <sub>5</sub>	25.2 <sub>0</sub>	58.2 <sub>6</sub>	64.4 <sub>2</sub>							111
39b 	D <sub>2</sub> O	51.5 <sub>4</sub> (a) 44.8 <sub>5</sub> (eq)	68.1 <sub>0</sub>	25.2 <sub>7</sub> 25.0 <sub>5</sub>	32.3 <sub>9</sub>	64.5 <sub>4</sub>							Present
41 	CDCl <sub>3</sub>	40.5 <sub>1</sub>	59.8 <sub>8</sub>	36.7 <sub>9</sub>	25.8 <sub>9</sub>	68.1 <sub>3</sub>	132.8 <sub>1</sub>	130.9 <sub>8</sub>	129.4 <sub>7</sub>	129.9 <sub>0</sub>	165.8 <sub>3</sub>		Present
41a 	D <sub>2</sub> O	39.4 <sub>3</sub>	62.3 <sub>6</sub>	34.7 <sub>9</sub>	24.7 <sub>1</sub>	65.3 <sub>2</sub>	133.5 <sub>2</sub>	129.3 <sub>6</sub>	128.7 <sub>9</sub>	129.3 <sub>6</sub>	165.3 <sub>5</sub>		Present



The Carbon-13 Chemical Shifts of Tropane Derivatives







Compound	Solvent	N-Me	C-1,5-	C-2,4	C-6,7	C-3	C-9	C-9	C-m	C-p	C=O	$\frac{C_{Ester}}{CH_2/CH_3}$	Reference
42 	CDCl <sub>3</sub>	39.7 <sub>3</sub>	60.3 <sub>7</sub>	35.8 <sub>7</sub>	26.7 <sub>0</sub>	67.8 <sub>6</sub>	132.7 <sub>1</sub>	129.5 <sub>3</sub>	128.2 <sub>8</sub>	129.9 <sub>6</sub>	165.3 <sub>5</sub>		Present
42a 	D <sub>2</sub> O	38.9 <sub>1</sub>	63.8 <sub>3</sub>	35.4 <sub>5</sub>	24.4 <sub>5</sub>	65.6 <sub>6</sub>	134.4 <sub>5</sub>	130.0 <sub>2</sub>	129.2 <sub>4</sub>	129.6 <sub>4</sub>	167.4 <sub>0</sub>		Present
43 	CDCl <sub>3</sub>	39.4 <sub>3</sub>	64.2 <sub>5</sub>	37.1 <sub>2</sub>	24.9 <sub>2</sub>	33.6 <sub>1</sub>	142.5 <sub>3</sub>	128.8 <sub>2</sub>	127.8 <sub>0</sub>	127.1 <sub>0</sub>			Present
43 	D <sub>2</sub> O	38.9 <sub>0</sub>	64.5 <sub>8</sub>	37.2 <sub>3</sub>	24.0 <sub>2</sub>	32.1 <sub>6</sub>	143.2 <sub>3</sub>	129.1 <sub>6</sub>	127.3 <sub>8</sub>	127.3 <sub>8</sub>			Present
44 	CDCl <sub>3</sub>	39.1 <sub>1</sub>	62.9 <sub>0</sub>	32.5 <sub>8</sub>	24.2 <sub>2</sub>	29.6 <sub>1</sub>	( )	128.6 <sub>6</sub>	126.3 <sub>4</sub>	126.3 <sub>4</sub>			Present
44 	D <sub>2</sub> O	38.4 <sub>2</sub>	63.1 <sub>3</sub>	33.0 <sub>7</sub>	23.4 <sub>8</sub>	29.5 <sub>2</sub>	( )	128.6 <sub>7</sub>	126.7 <sub>8</sub>	126.5 <sub>1</sub>			Present



TABLE XII (cont'd)

## The Carbon-13 Chemical Shifts of Tropane Derivatives








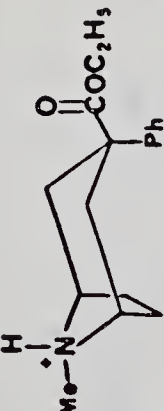
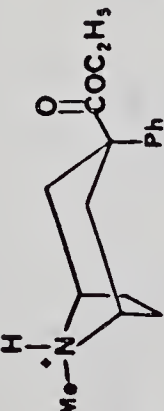
Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=O	C <sup>Ester</sup> CH <sub>2</sub> /CH <sub>3</sub>	Reference
45	CDCl <sub>3</sub>	39.27	58.80	41.48	27.19	71.69					174.79	52.33	Present
													
45	MeOH-d <sub>4</sub>	38.57	60.80	39.76	25.68	71.59					175.60	52.76	Present
45a	CDCl <sub>3</sub>	37.76	62.04	38.25	24.06	69.70					173.44	53.08	Present
													
45a	MeOH-d <sub>4</sub>	38.25	63.60	39.27	24.06	69.91					174.57	53.35	Present
46	CDCl <sub>3</sub>	40.30	60.91	45.48	25.68	72.67	150.56	128.07	124.67	126.56			Present
													
46	MeOH-d <sub>4</sub>	40.57	62.20	46.02	25.94	72.99	151.81	128.72	125.64	127.04			Present








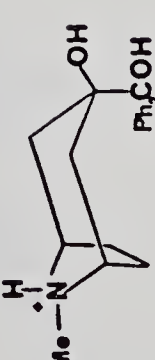
TABLE XII (cont'd)

## The Carbon-13 Chemical Shifts of Tropane Derivatives

Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-9	C-8	C-m	C-p	C-o	Ester CH <sub>2</sub> /CH <sub>3</sub>	Reference
46a 	MeOH-d <sub>4</sub>	39.6 <sub>5</sub>	64.2 <sub>0</sub>	44.7 <sub>8</sub>	25.1 <sub>9</sub>	71.9 <sub>6</sub>	150.0 <sub>8</sub>	129.0 <sub>9</sub>	125.8 <sub>0</sub>	127.8 <sub>0</sub>			Present
46a 	D <sub>2</sub> O	38.8 <sub>5</sub>	63.6 <sub>7</sub>	43.0 <sub>0</sub>	23.4 <sub>7</sub>	70.9 <sub>5</sub>	147.4 <sub>4</sub>	128.8 <sub>9</sub>	124.5 <sub>7</sub>	127.7 <sub>5</sub>			Present
47 	CDCl <sub>3</sub>	39.8 <sub>1</sub>	59.0 <sub>2</sub>	41.4 <sub>8</sub>	28.2 <sub>1</sub>	46.0 <sub>7</sub>	142.5 <sub>8</sub>	128.1 <sub>2</sub>	126.7 <sub>2</sub>	126.6 <sub>1</sub>	175.3 <sub>8</sub>	60.3 <sub>7</sub> 14.2 <sub>4</sub>	Present
47 	MeOH-d <sub>4</sub>	39.7 <sub>0</sub>	60.5 <sub>3</sub>	40.1 <sub>4</sub>	27.2 <sub>4</sub>	( )	142.7 <sub>4</sub>	128.9 <sub>3</sub>	127.6 <sub>9</sub>	127.6 <sub>9</sub>	176.9 <sub>4</sub>	61.5 <sub>0</sub> 14.2 <sub>4</sub>	Present
47a 	CDCl <sub>3</sub>	38.7 <sub>3</sub>	62.9 <sub>0</sub>	33.9 <sub>3</sub>	22.9 <sub>8</sub>	44.7 <sub>8</sub>	138.5 <sub>9</sub>	128.5 <sub>5</sub>	126.7 <sub>7</sub>	127.7 <sub>4</sub>	173.3 <sub>8</sub>	61.3 <sub>3</sub> 13.7 <sub>0</sub>	Present
47a 	MeOH-d <sub>4</sub>	38.7 <sub>9</sub>	64.2 <sub>5</sub>	35.2 <sub>8</sub>	23.3 <sub>0</sub>	45.8 <sub>0</sub>	139.6 <sub>1</sub>	129.4 <sub>2</sub>	127.9 <sub>6</sub>	128.6 <sub>6</sub>	175.0 <sub>0</sub>	62.3 <sub>1</sub> 13.9 <sub>7</sub>	Present









The Carbon-13 Chemical Shifts of Tropane Derivatives

Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=O	C-Ester CH <sub>2</sub> /CH <sub>3</sub>	Reference
48 	MeOH-d <sub>4</sub>	38.6 <sub>0</sub>	64.4 <sub>4</sub>	36.4 <sub>4</sub>	23.0 <sub>6</sub>	47.5 <sub>0</sub>	141.4 <sub>0</sub>	129.1 <sub>2</sub>	127.5 <sub>5</sub>	127.8 <sub>2</sub>	168.4 <sub>5</sub>		Present
48a 	MeOH-d <sub>4</sub>	38.9 <sub>7</sub>	64.0 <sub>6</sub>	35.0 <sub>4</sub>	22.9 <sub>0</sub>	46.9 <sub>6</sub>	138.8 <sub>2</sub>	129.2 <sub>8</sub>	127.6 <sub>1</sub>	128.5 <sub>8</sub>	177.8 <sub>1</sub>		Present
48a 	D <sub>2</sub> O	38.2 <sub>1</sub>	63.1 <sub>8</sub>	34.5 <sub>3</sub>	22.2 <sub>3</sub>	44.8 <sub>4</sub>	138.3 <sub>8</sub>	128.9 <sub>4</sub>	127.1 <sub>6</sub>	128.1 <sub>8</sub>	177.8 <sub>7</sub>		Present
49 	CDCl <sub>3</sub>	40.0 <sub>3</sub>	58.9 <sub>1</sub>	41.9 <sub>7</sub>	28.9 <sub>7</sub>	(75.6 <sub>9</sub> )	145.0 <sub>6</sub>	128.2 <sub>8</sub>	127.2 <sub>6</sub>	126.5 <sub>0</sub>		C-3' (80.1 <sub>1</sub> )	Present
49 	MeOH-d <sub>4</sub>	40.4 <sub>0</sub>	60.0 <sub>4</sub>	42.5 <sub>6</sub>	29.4 <sub>5</sub>	(77.1 <sub>4</sub> )	(146.6 <sub>3</sub> )	129.5 <sub>2</sub>	127.7 <sub>4</sub>	126.9 <sub>9</sub>		C-3' (80.3 <sub>7</sub> )	Present
49a 	MeOH-d <sub>4</sub>	39.2 <sub>6</sub>	62.6 <sub>8</sub>	40.4 <sub>6</sub>	28.3 <sub>8</sub>	(76.1 <sub>7</sub> )	(145.0 <sub>1</sub> )	129.3 <sub>6</sub>	128.6 <sub>6</sub>	128.0 <sub>7</sub>		C-3' (80.9 <sub>2</sub> )	Present



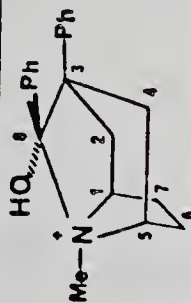
The Carbon-13 Chemical Shifts of Tropane Derivatives

Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=O	$\delta_{\text{CH}_2/\text{CH}_3}^{\text{Ester}}$	Reference
 49a	D <sub>2</sub> O	38.7 <sub>4</sub>	61.1 <sub>8</sub>	39.1 <sub>7</sub>	27.2 <sub>0</sub>	(74.8 <sub>8</sub> )	(142.8 <sub>6</sub> )	128.1 <sub>8</sub>	128.1 <sub>8</sub>	128.1 <sub>8</sub>		C-3' (80.8 <sub>2</sub> )	Present
 3	CDCl <sub>3</sub>	39.4 <sub>9</sub>	58.1 <sub>0</sub>	44.8 <sub>3</sub>	29.2 <sub>9</sub>	50.3 <sub>9</sub>	(141.8 <sub>8</sub> ) (141.6 <sub>8</sub> )	(128.9 <sub>8</sub> ) (128.4 <sub>5</sub> )	(127.4 <sub>7</sub> ) (127.1 <sub>5</sub> )	(126.6 <sub>1</sub> ) (127.1 <sub>5</sub> )	202.6 <sub>2</sub>		Present
 3	CD <sub>2</sub> Cl <sub>2</sub>	39.7 <sub>0</sub>	58.4 <sub>2</sub>	45.2 <sub>6</sub>	29.6 <sub>7</sub>	50.6 <sub>1</sub>	(142.4 <sub>2</sub> ) (142.2 <sub>0</sub> )	(129.2 <sub>0</sub> ) (128.7 <sub>2</sub> )	(127.7 <sub>4</sub> ) (127.4 <sub>8</sub> )	(126.8 <sub>8</sub> ) (127.4 <sub>8</sub> )	202.6 <sub>7</sub>		Present
 3	MeOH-d <sub>4</sub>	39.9 <sub>5</sub>	69.6 <sub>5</sub>	41.1 <sub>1</sub>	27.4 <sub>0</sub>	52.4 <sub>0</sub>							Present
 3a	CDCl <sub>3</sub>	38.7 <sub>3</sub>	63.4 <sub>4</sub>	35.9 <sub>3</sub>	22.9 <sub>8</sub>	50.0 <sub>1</sub>					202.4 <sub>1</sub>		Present
 3a	MeOH-d <sub>4</sub>	39.0 <sub>0</sub>	64.5 <sub>7</sub>	37.0 <sub>6</sub>	23.5 <sub>2</sub>	(f)					(f)		Present

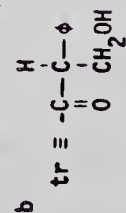


The Carbon-13 Chemical Shifts of Tropane Derivatives

Compound	Solvent	N-Me	C-1,5	C-2,4	C-6,7	C-3	C-q	C-o	C-m	C-p	C=O	C <sub>Ester</sub> CH <sub>2</sub> /CH <sub>3</sub>	Reference
3b ~	MeOH-d <sub>4</sub>	37.06	(C-1) 67.38	(C-2) 40.30	C-6 30.59	C- 52.60					C-8 109.41		Present
			(C-8) 74.82	(C-4) 44.40	C-7 26.54								



<sup>a</sup> Solvent not reported.



<sup>c</sup> High field resonance (CH<sub>3</sub>): low field resonance (CH<sub>2</sub>).

<sup>d</sup> Parenthesis indicate some uncertainty in assignment.

<sup>e</sup> An equilibrium mixture.

<sup>f</sup> Not observable due to low concentration of this fraction.

<sup>g</sup> Resonance C-3' 66.0<sub>3</sub> ppm.



hydrochloride  $\underset{\sim}{3a}$  and  $\underset{\sim}{3b}$ .

## C. DISCUSSION

### 1. Additivity Effects

The preferred conformation of the tropane ring is a chair<sup>106</sup>. Introduction of a carbonyl at C-3 as in ( $\underset{\sim}{34}$ ) results in an  $\alpha$ -carbonyl substituent effect at C-2,4 of -17.2 ppm which is larger than observed in the piperidines<sup>43</sup> (-14.7 ppm) and cyclohexanes<sup>105b</sup> (-13.4 ppm). This may be due in part to the rigidity in the tropane system. Both axial and equatorial hydroxyl substituent parameters may be derived by comparing the carbon chemical shifts in  $\underset{\sim}{33}$ ,  $\underset{\sim}{37}$  and  $\underset{\sim}{38}$  determined in  $CDCl_3$ . The values are: equatorial:  $\alpha$ , +46.8;  $\beta$ , +8.4;  $\gamma$ , -1.1 and  $\delta_{C-6,7}$  +1.1 ppm, axial:  $\alpha$ , +47.9;  $\beta$ , +9.5;  $\gamma$ , -0.9 and  $\delta_{C-6,7}$  +0.4 ppm. Of greatest significance is the similarity between the  $\alpha$ - and  $\gamma$ -effects for the different hydroxyl configurations. The analogous effects differ widely in cyclohexanes<sup>105a</sup> (equatorial:  $\alpha$ , +43.2 and  $\gamma$ , -1.1 ppm; axial:  $\alpha$ , +37.8 and  $\gamma$ , -6.8 ppm) as well as in piperidines. (equatorial<sup>94</sup>:  $\alpha$ , +42.6 and  $\gamma$ , -2.7 ppm, axial<sup>55</sup>:  $\alpha$ , +28.1 and  $\gamma$ , -4.7 ppm). It is possible that there exists a contribution of the boat form in  $\underset{\sim}{38}$  due to severe 1,3-diaxial interactions in the chair conformer. Further, comparison of the C-6,7 carbon resonances in  $\underset{\sim}{37}$  and  $\underset{\sim}{38}$  indicates an hydroxyl  $\delta$ -shielding of 0.7 ppm in contrast to the deshielding effect expected (2.6 ppm)<sup>37</sup>. These data suggest contributions from the boat conformer of  $\underset{\sim}{38}$ . Equatorial phenyl substituent parameters are obtained from comparison of  $\underset{\sim}{38}$  and  $\underset{\sim}{46}$ ,  $\alpha$ , +9.1;  $\beta$ , +6.4 and  $\gamma$ , +1.1 ppm. Compared with the analogous parameters obtained in 4-phenylpiperidines<sup>55</sup>,  $\alpha$ , +17.7,  $\beta$ , +6.7 and  $\gamma$ , -0.3 ppm, a large decrease in the  $\alpha$ -effect is observed.



The contributions from the boat conformer in  $\tilde{38}$  may again account for these parameters differing. Introduction of the ethylene bridge to the piperidine ring induces the carbon-13 chemical shifts given in Table XIII. The  $\alpha$ -effect of +7.0 ppm in piperidine can be taken as the representative value for the introduction of the ethylene bridge with the attenuation to +4.5 and +4.9 ppm in N-methylpiperidine and N-methyl-4-piperidone, respectively, due to the steric interaction of the ethylene bridge with the N-methyl group. The large  $\alpha$ -effect of +9.2 ppm in N-methyl-4-phenyl-4-piperidinol may be attributable to the axial hydroxyl group. The  $\beta$ -effects remain questionable under any circumstance. The  $\gamma$ -effect on C-4 of -8.0 ppm can be taken as a representative value with the shielding being greatly attenuated in N-methyl-4-piperidone (+0.2 ppm) as expected. The deshielding  $\gamma$ -effect of 2.6 ppm in N-methyl-4-phenyl-4-piperidinol may be attributed to the axial hydroxyl group. The  $\gamma$ -effect at the N-methyl group has an average value of -6.5 ppm.

## 2. Tropane Conformations

### a. Protonation Effects

In order to determine the conformation of the tropanes both their free base and protonated forms were studied. The protonation effects are summarized in Table XIV.

It is well established<sup>112,113,114</sup> that 3-phenyl-3-tropinol  $\tilde{46}$  and its corresponding hydrochloride  $\tilde{46a}$  exist preferentially in the chair conformation. Consequently "chair" protonation effects in the tropane system can be determined using this compound as a model, i.e.,  $\beta_{N-Me}$  -0.9,  $\beta_{C-1,5}$  +2.0,  $\gamma_{C-2,4}$  -1.2,  $\gamma_{C-6,7}$  -0.8 and  $\delta_{C-3}$  -1.0 ppm. However, if the tropane ring exists in a boat conformation in the free



TABLE XIII

Additivity Effects of the Introduction of the C-6,7 EthyleneBridge to the Piperidine Ring System



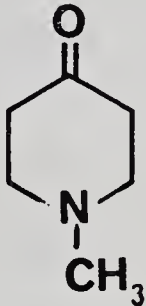
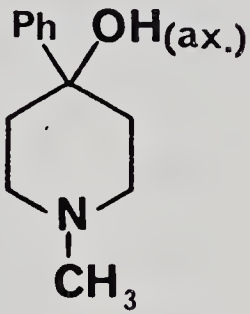
Effect	Structure			
				
$\alpha$	+7.0	+4.5	+4.9	+9.2
$\beta$	+5.4	+3.8	+6.2	+7.1
$\gamma_{C-4}$	-8.3	-8.0	+0.2	+2.6
$\gamma_{N-Me}$	-	-6.5	-7.5	-6.0



TABLE XIV

Protonation Effects on the Carbon-13 Chemical Shifts inVarious Tropanes

Compound	Solvent	Carbon Position and Effect				
		$\beta(\text{N-Me})$	$\beta(\text{C-1,5})$	$\gamma(\text{C-2,4})$	$\gamma(\text{C-6,7})$	$\delta(\text{C-3})$
45	$\text{CDCl}_3$	-1.5	+3.2	-3.3	-3.1	-2.0
47	$\text{CDCl}_3$	-0.1	+3.9	-7.6	-5.3	-1.3
3	$\text{CDCl}_3$	-0.8	+5.3	-8.9	-6.3	-0.4
45	$\text{MeOH-d}_4$	-0.3	+2.8	-0.5	-1.6	-1.7
46	$\text{MeOH-d}_4$	-0.9	+2.0	-1.2	-0.8	-1.0
47	$\text{MeOH-d}_4$	-0.9	+3.7	-4.9	-3.9	
48	$\text{MeOH-d}_4$	+0.4	-0.4	-1.4	-0.2	-0.5
49	$\text{MeOH-d}_4$	-1.1	+2.6	-2.1	-1.1	-1.0
Average values		-0.7	+2.9	-3.7	-2.8	-1.1



base and protonation induces a conformational change different protonation effects are expected.

The major effect upon protonation in this situation will be to produce a  $\gamma$ -shielding effect at C-6,7 in the protonated chair conformation (Figure 9b) as a result of interaction with the added axial C-3 substituent. Any deviations from this  $\gamma$ -effect are expected to reflect a change from preferred chair (Figure 9b) to preferred boat conformer (Figure 9c) in the protonated tropane molecule. A shielding effect at C-1,5 is also expected in the boat conformer, the consequence of eclipsing between the 1(5) and 2(4) hydrogen atoms. Therefore, referring to Figure 9, if the chair conformation (Figure 9b) predominates in the protonated form a relief of the hydrogen interactions will produce an increased deshielding of the C-1,5 carbon atoms compared to those in the protonated boat conformation (Figure 9c). Utilizing these protonation aspects, the tropane conformations can be discussed.

#### i. Ecgonine Methyl Ester (45)

Both pmr and infrared spectral data provide evidence<sup>24</sup> that in solution the boat conformation of 45 is significantly populated. Therefore, the protonation effects observed in the carbon-13 spectrum of 45a refer to the protonated boat conformer of the free base 45 (Figure 9a). These effects are small (Table XIV) and no  $\gamma$ -effect (as discussed earlier) is observed. As far as the carbon-13 results are concerned the magnitude of the protonation effects are not large enough to invoke a conformational change (Figure 9b) but rather a change in the orientation of the hydroxyl O-H bond with concomitant intra-molecular hydrogen bonding between the N-H proton and oxygen is indicated. The boat



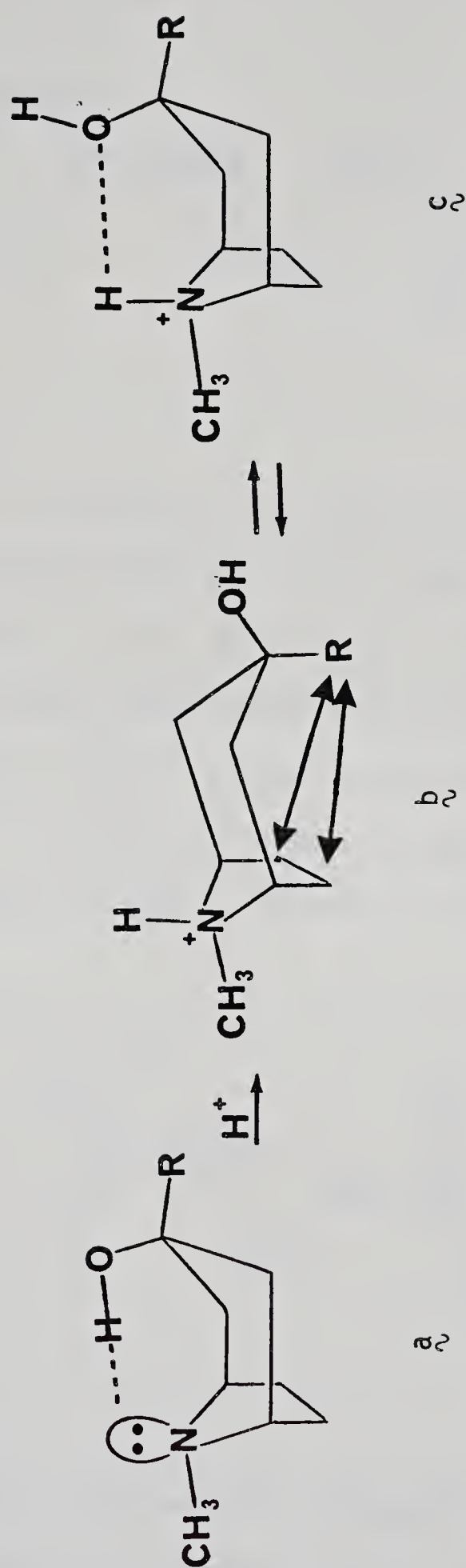
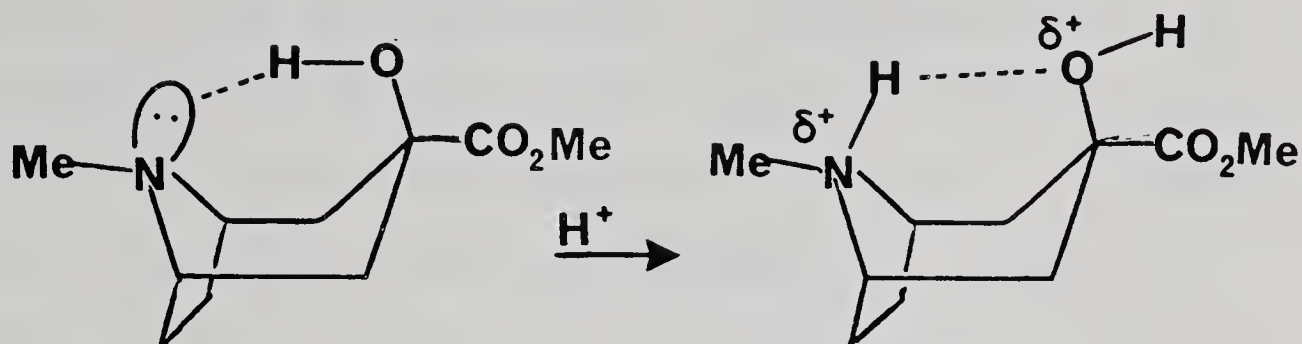


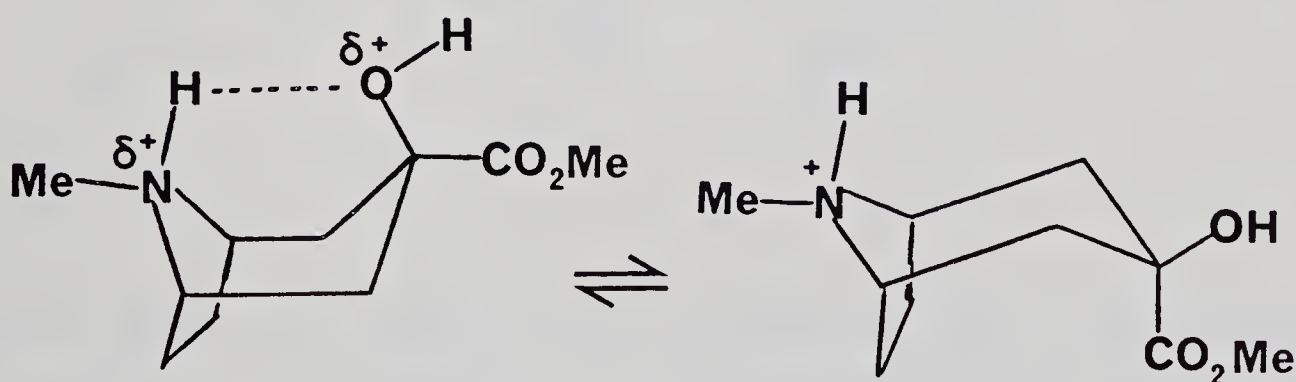
FIGURE 9: Suggested conformational aspects on protonation of a tropane molecule existing in a preferred boat conformation in  $\tilde{a}$  (free base) and  $\tilde{c}$  (hydrochloride) due to the intramolecular hydrogen bonding nature of the hydroxyl group.



structure is thus maintained. Comparison of the effects of protonation



of  $\underline{45}$  for solutions in methanol- $d_4$  and chloroform- $d_1$  show that much larger protonation effects occur in the less polar solvent. In particular, C-6,7 is shielded -3.1 ppm and -1.6 ppm in  $CDCl_3$  and  $MeOH-d_4$ , respectively, indicating a contribution from the chair conformer of  $\underline{45a}$  in the former solvent. That is, a  $\gamma$ -shielding effect occurs at C-6,7. It is suggested that the protonated species ( $\underline{45a}$ ) be represented by the equilibrium: the boat conformer is favoured in methanol and the chair



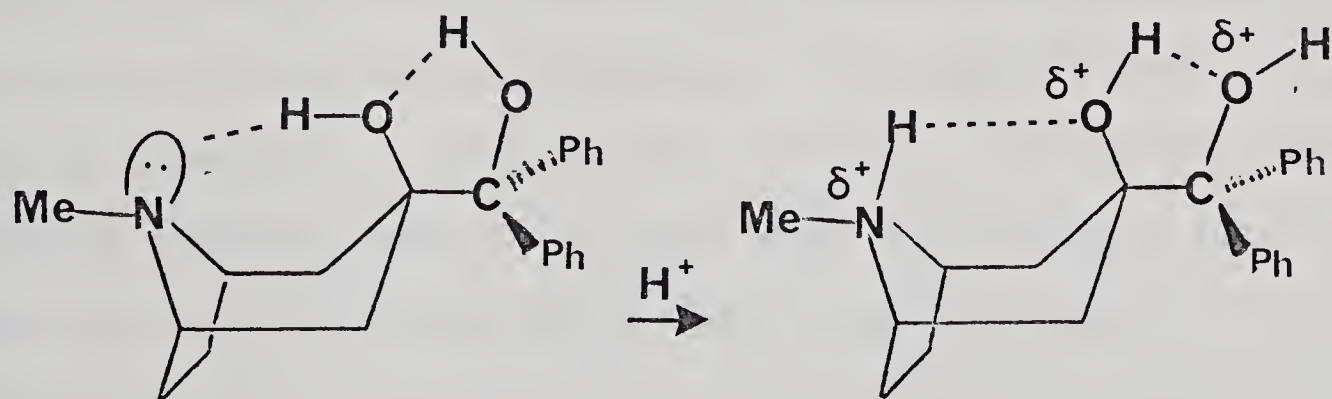
conformer in chloroform. The methanol, being more polar, is better able to solvate the partially charged centers at the nitrogen and oxygen atoms. The chemical shifts observed for the hydrochloride are, therefore,



average values. The protonation effects of  $\underset{\sim}{45}$  in chloroform are explained as follows. The deshielding (+3.2 ppm) at C-1,5 is attributed to a greater amount of 'formal charge' on the nitrogen when in the chair conformer than the boat conformer where the charge is expected to be delocalized over both the nitrogen and oxygen atoms. In addition, the interaction between the eclipsed hydrogens are relieved. The shielding effect (-3.3 ppm) at C-2,4 is a result of both a change in conformation to the chair conformer together with the presence of a more pronounced  $\gamma$ -effect of the  $\overset{\oplus}{\text{N}}\text{-H}$  proton.

ii.  $3\alpha$ -Diphenylhydroxymethyl- $3\beta$ -tropanol ( $\underset{\sim}{49}$ )

The effects of protonation in  $\underset{\sim}{49}$  can be explained in a similar manner with intra-molecular hydrogen bonding possible in the hydrochloride ( $\underset{\sim}{49a}$ ) with the boat form predominating. The larger



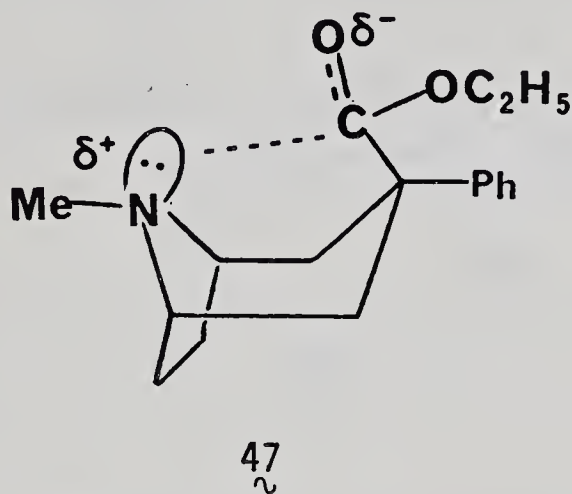
protonation effect (-2.1 ppm) at C-2,4, compared to that in  $\underset{\sim}{45}$  (-0.5 ppm), can be attributed to a difference in the equilibria for the hydrochlorides  $\underset{\sim}{49a}$  and  $\underset{\sim}{45a}$ . The chair form is dominant in the former resulting in the 2.1 ppm shielding at C-2,4 as a result of a  $\gamma$ -effect of the  $\overset{\oplus}{\text{N}}\text{-H}$  proton.

iii. Ethyl  $3\alpha$ -phenyltropane- $3\beta$ -carboxylate ( $\underset{\sim}{47}$ )

The hydrochloride of  $\underset{\sim}{47}$  studied in methanol shows large



protonation effects at C-1,5 (+3.7 ppm), C-2,4 (-4.9) and C-6,7 (-3.9 ppm). The pmr study<sup>24</sup> did not indicate any boat structure for this molecule. However, the <sup>13</sup>C data indicate contributions from the boat conformer in the free base (47). This can be explained in two ways.

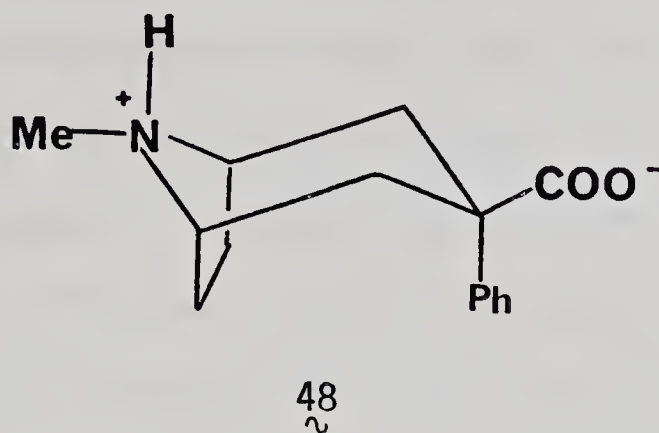


First, the large increase in protonation effects from 46 to 47, which should be of similar magnitude if chair forms existed in both structures, can only be explained if a conformational change occurred between the free base and hydrochloride derivatives of 47. The acid derivative (47a) is expected to be predominately in the chair form since no intramolecular hydrogen bonding of the type found in 45 and 49 is possible. Hence the large protonation effects must be due to a change to the chair conformer in 47a with shielding at C-6,7 and deshielding at C-1,5. A large shielding (4.9 ppm) at C-2,4 in 47 also occurs upon protonation and is attributed to the conformational change in addition to the expected  $\gamma$ -effect. Second, the similarity in the magnitude of the protonation effects in 47 and 3. The boat conformation of the latter base is established<sup>11</sup>, thus similar conformations for 47 and 3 are indicated.



iv. 3 $\alpha$ -Phenyltropane-3 $\beta$ -carboxylic acid (48)

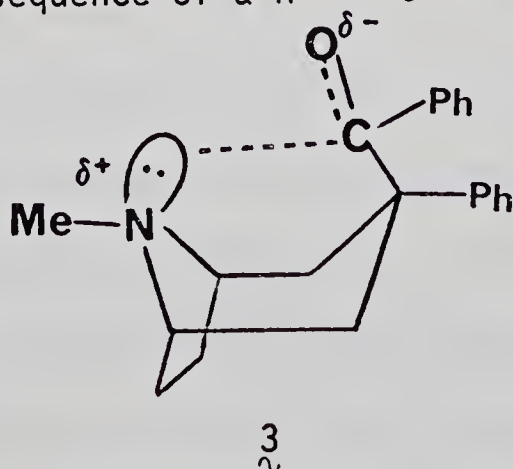
Based on the protonation effects observed in the carbon-13 spectra, a Zwitterion is proposed for the free base 48. This proposal



is based on the small chemical shift differences observed upon protonation at all the carbon positions except at C-8 (+9.3 ppm) and C-2,4 (-1.4 ppm). The large deshielding at C-8 is due to a change from the carboxylate anion in the zwitterion (48) to the protonated form in the acid (48a). The shielding at C-2,4 is due to a change in the  $\gamma$ -effect, on those carbon atoms, of O<sup>-</sup> to OH upon introduction of the proton.

v. 3 $\alpha$ -Phenyl-3 $\beta$ -tropanyl phenyl-ketone (3)

The large protonation effects (C-1,5 +5.3, C-2,4 -8.9 and C-6,7 -6.3 ppm) observed in 3 indicate a change in conformation in the compound. It is established that the free base, (3) exists in a boat conformation as a consequence of a N $\cdots\cdots$ C $\cdots\cdots$ O interaction:





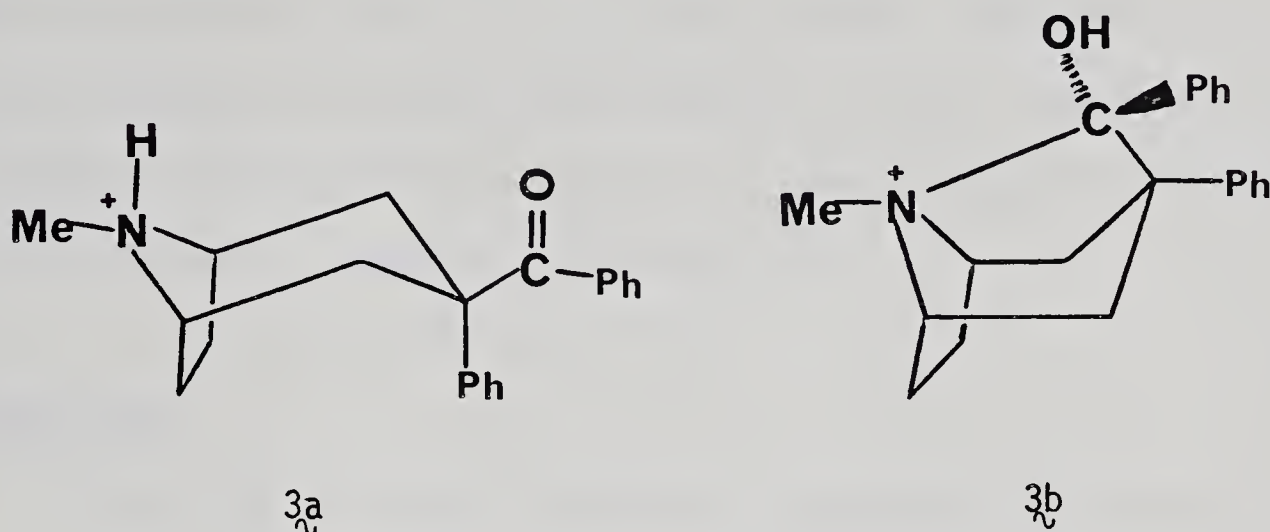
Therefore, a chair conformer (Figure 9b) is expected in the hydrochloride ( $3a$ ) since the possibility of intra-molecular hydrogen bonding as in  $45a$  and  $49a$  is not possible in  $3a$  due to the substituents at C-3 being unable to form a stable intra-molecular hydrogen bonded molecule. Therefore, a change in conformation from a boat conformer in the free base to a chair in the hydrochloride is invoked. As already stated, no conformational changes are evident in  $46$  upon protonation, therefore, if we assume solvent effects are minimal, subtraction of the protonation effects for  $46$  from the average values for  $47$  and  $3$  give values for the conformational differences in  $47$  and  $3$ . That is, N-Me, +0.5, C-1,5, +2.5, C-2,4, -7.0, C-6,7, -5.0 and C-3, 0.0 ppm for going from a boat conformer to a chair conformer. The major effects are as expected. C-1,5 is deshielded (2.6 ppm) as a consequence of removal of the eclipsing hydrogen, C-6,7 is shielded (5.0 ppm) due to the introduction of the steric interaction of the C-3 axial substituent and C-2,4 is shielded (7.0 ppm) due to the introduction of a  $\gamma$ -gauche interaction at these carbon atoms with the  $\text{N}^{\oplus}\text{-H}$  proton.

The effect of solvent change on the spectral behaviour of the  $\text{N}\cdots\cdots\text{C}\cdots\cdots\text{O}$  interaction in  $3$  should be noted. The carbon chemical shifts are similar in both  $\text{CDCl}_3$  and  $\text{CD}_2\text{Cl}_2$ . However, when  $\text{MeOH-d}_4$  was used as solvent large chemical shift differences are observed. C-1,5 and C-3 are deshielded (+11.5 and +2.0 ppm, respectively) and C-2,4 and C-6,7 are shielded (3.7 and 2.3 ppm, respectively) the N-methyl resonance is unaffected compared to the chemical shifts determined in  $\text{CDCl}_3$ . The behaviour of  $3$  in methanol is a result of a greater degree of nitrogen-carbonyl interaction in this solvent than in  $\text{CDCl}_3$ , the methanol being better able to stabilize, by an appropriate solvation



mechanism, the partial charge separation which is produced by this interaction. A similar argument has been used to explain the change in UV absorption of  $3_{\sim}^{11}$ .

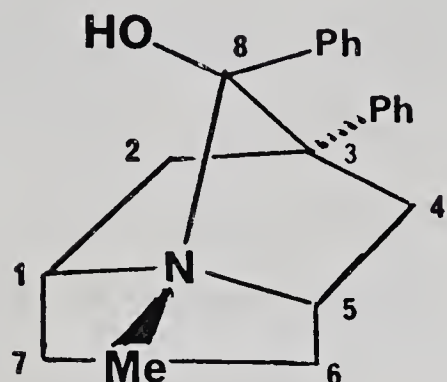
Similar solvent effects occur for the hydrochloride of  $3_{\sim}$ . In methanol large chemical shift differences arise. Bell and Archer have suggested<sup>11</sup> that this hydrochloride, in methanol, is a mixture which consists mainly of the form with 'formally bonded' nitrogen and carbonyl function ( $3b$ ) in equilibrium with the form possessing the normal ketone  $3a$ . This is verified in the carbon-13 spectra by the occurrence of the



resonance at 109.4<sub>1</sub> ppm due to C-8, now an hydroxyl carbon, and also by the I.R. spectra which exhibits absorption bands at 3400 cm<sup>-1</sup> and 1675 cm<sup>-1</sup> attributable to hydroxyl and carbonyl functions, respectively. The assignment of the carbon resonances in  $3a/3b$  was facilitated by a change in the equilibrium concentration between two spectral determinations. The chemical shifts of  $3a$  are similar to those obtained for the solution in CDCl<sub>3</sub> (<1 ppm difference) and enable assignment of the shifts due to the chair conformation in the equilibrium mixture. The formation of the N-C<sub>8</sub> bond generates an assymetric center at C-8. Hence each carbon in the molecule  $3b$  gives rise to an individual resonance. Structure  $3b$



can be represented as a norbornyl derivative:



Unfortunately the carbon chemical shift of the analogous norbanyl system without the ethylene bridge have not been reported. Therefore, the distinction between the methine and methylene carbons is based only on the assumption that the hydroxyl group will exert a larger  $\gamma$ -shielding effect at C-1 and C-2 compared to C-5 and C-4.

#### D. CONCLUSIONS

This study of tropane derivatives successfully clarifies the assignments of the methylene carbons, C-2,4 and C-6,7 and provides a better insight into the conformations of several tropane systems. Carbonyl and hydroxyl additivity parameters in the tropane series (carbonyl  $\alpha$  effect -17.2 ppm, equatorial hydroxyl:  $\alpha$  +46.8,  $\gamma$  -1.1 ppm, axial hydroxyl:  $\alpha$  +47.9,  $\gamma$  -0.9 ppm) differ from those in the analogous piperidine [carbonyl(-14.7 ppm), equatorial hydroxyl  $\alpha$  +42.6 and  $\gamma$  -2.7 ppm and axial hydroxyl  $\alpha$  +28.1 and  $\gamma$  -4.7 ppm, respectively.]. On the basis of these effects evidence is presented for boat contributions to the conformation of tropine ( $\sim$ 38).

The intra-molecular hydrogen bonding present in the three tropanes, ecgonine methyl ester ( $\sim$ 45), 3 $\alpha$ -diphenylhydroxymethyl-3 $\beta$ -



tropanyl phenyl ketone ( $\underset{\sim}{3}$ ) suggested by Casy et al.<sup>24</sup> was clarified by comparing the protonation effects observed in the carbon-13 spectra. The conformational change from boat to chair conformers is best exemplified in  $\underset{\sim}{47}$  and  $\underset{\sim}{3}$ . The change is calculated by observing shielding at C-6,7 (5.0 ppm) and C-2,4 (7.0 ppm) and deshielding at C-1,5 (2.5 ppm). No effect is observed at the carbonyl carbon. The hydrochloride derivatives of  $\underset{\sim}{45}$  and  $\underset{\sim}{49}$  are also present in boat conformations for solutions in methanol but an equilibrating mixture is observed in less polar media ( $\text{CDCl}_3$ ) with the chair conformation predominating. It is suggested that  $\underset{\sim}{47}$  exists preferentially as a boat conformer with a strong nitrogen-carbonyl interaction similar to that found in  $\underset{\sim}{3}$ . The hydrochloride,  $\underset{\sim}{3a}$ , dissolved in methanol is a ketone/alcohol equilibrium mixture as shown by the carbon-13 spectra. Evidence is presented for a zwitterion in 3 $\alpha$ -phenyltropane-3 $\beta$ -carboxylic acid ( $\underset{\sim}{48}$ ).

## E. EXPERIMENTAL

Dr. J. E. Coates supplied samples of  $\underset{\sim}{36}$ ,  $\underset{\sim}{43}$ - $\underset{\sim}{49}$  and  $\underset{\sim}{3}$ . The hydrochloride of 3 $\alpha$ -phenyl-3 $\beta$ -tropanyl phenyl ketone  $\underset{\sim}{3}$  was isolated by bubbling anhydrous HCl into an ether solution of the free base. A white precipitate of mp 254-257° was obtained (mp lit.<sup>11</sup> 257-257.5°).

The free base, 3 $\alpha$ -phenyltropane-3 $\beta$ -carboxylic acid ( $\underset{\sim}{48}$ ) was prepared by the addition of a 5% sodium hydroxide solution to 3 $\alpha$ -phenyltropane-3 $\beta$ -carboxylic acid·HCl ( $\underset{\sim}{48a}$ ) dissolved in a minimum amount of water, extraction with chloroform, dried over  $\text{MgSO}_4$  and evaporated to dryness afforded white crystals, mp 121-122° (mp lit.<sup>115</sup> 121-122.5°).



## CHAPTER IV

### PHOSPHORUS HETEROCYCLES

#### A. INTRODUCTION

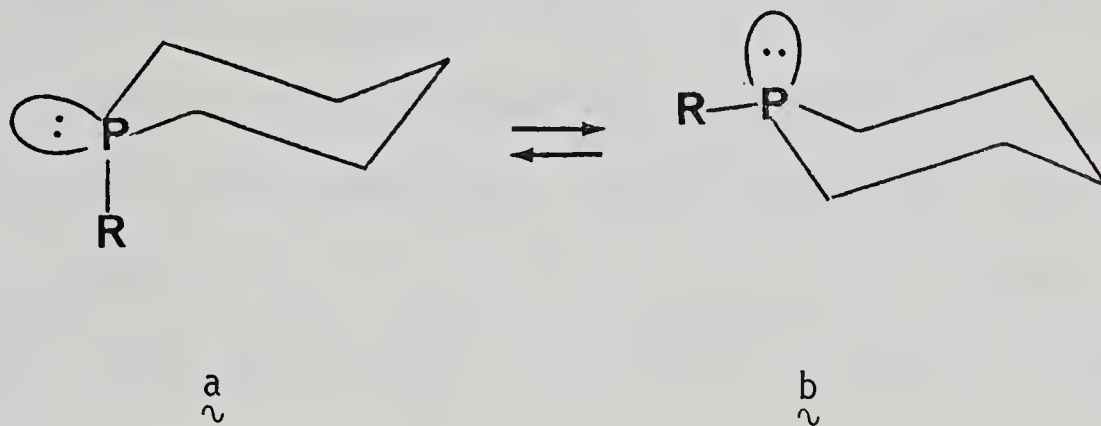
Carbon-13 nmr spectroscopy has been employed with much success to six-membered nitrogen heterocyclic compounds. However, until very recently little was known concerning  $^{13}\text{C}$  chemical shift parameters in rings containing a phosphorus atom. We attempted to rectify this situation in the present study by relating structural and stereochemical features to carbon-13 chemical shifts and  $J_{\text{CP}}$  coupling constants. Our work has been complemented by the very recent work of Quin and co-workers<sup>73a,b,74</sup>. These authors have concentrated on the use of  $^{13}\text{C}$  nmr spectroscopy to determine the structures of the cis- and trans-isomers of the 1,4-disubstituted-4-phosphorinanol<sup>74</sup>, and the chair-to-chair inversion equilibria of selected 1-substituted phosphorinanes and their corresponding sulphides<sup>73a,b</sup>. Our studies have concentrated on the effect of substituents at the C-2,6 and C-3,5 positions on the conformation and chair-to-chair interconversion of 1-phenyl-4-phosphorin -anes, -ones and -ols. The effects of oxide formation were also determined.

Carbon-13 nmr spectra of compounds containing phosphorus exhibit not only characteristic chemical shifts but also coupling between the phosphorus and carbon atoms through two and sometimes three bonds. The size of the two-bond coupling for trivalent phosphorus is apparently subject to steric control and consequently is of value in conformational analysis<sup>74,78</sup>. Further, carbon-13 coupling with



phosphorus exhibits distance<sup>74</sup> and directional<sup>74</sup> characteristics and, therefore, is a useful aid in carbon assignment.

The orientation of the phosphorus substituent is of conformational interest since in the phosphorinane system the  $\Delta H^\circ$  value is remarkably small for the equilibrium between  $\underset{\sim}{a}$  and  $\underset{\sim}{b}$  (-0.68 kcal/mole,



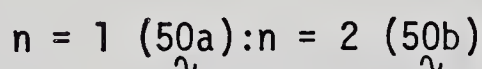
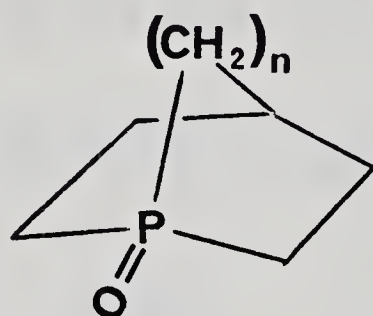
$R = CH_3$ )<sup>73a</sup>. A low-temperature  $^{31}P$  nmr study<sup>116</sup> on 1-methylphosphorinane gave a constant (0.56) for the conformational equilibrium at 25° indicating that the axial form predominates at room temperature. The magnitude of the  $^2J_{PC}$  coupling constant to the carbon atoms C-3,5 is apparently specifically related to the position of conformational equilibrium. Large  $^2J_{PC}$  values were observed<sup>74</sup> in systems where the dihedral angle between the phosphorus lone-pair orbital and the coupled carbon is small and vice-versa for large dihedral angles. For example, negligible coupling (0-1 Hz) occurs at C-3,5 in trans-1-methyl-4-*t*-butyl-4-phosphorinanol<sup>74</sup>, while significant coupling (7 Hz) occurs in the cis-isomer<sup>74</sup>.  $^2J_{PC}$  coupling values between the phosphorus atom and the carbons C-3,5 in the phosphorinanes studied in this work are compared to these limiting values to determine preferences in equilibria.

The present studies on the phosphorinanes indicate a maximum  $^2J_{PC}$  value (33 Hz) occurs when the dihedral angle between the phosphorus



lone pair orbital and the carbon two bonds removed is close to  $0^\circ$ . The coupling decreases (11 Hz) at a dihedral angle of about  $60^\circ$  and reduces to zero as the angle approaches  $180^\circ$ . We conclude that a Karplus type relationship probably holds between the dihedral angle and the  $^2J_{PC}$  coupling constants. However, in the absence of defined dihedral angles the implied relationship must remain qualitative.

A Karplus relationship may hold for the  $^3J_{PC}$  coupling values. However, in the phosphines the magnitude of this coupling is too small to be of any consequence. On the other hand,  $^3J_{PC}$  values increase on oxidation and a Karplus type relationship has been suggested<sup>117</sup> based on the bicyclic phosphine oxides  $\underset{\sim}{50a}$  and  $\underset{\sim}{50b}$ . The



contribution of the dipolar form of the phosphorus-oxygen bond can be estimated from the carbon-13 chemical shifts.

## B. RESULTS

The observed  $^{13}C$  chemical shifts for 1-phenyl-, and 1-phenyl-2,2,6,6-tetramethyl- phosphorinanes and their corresponding phosphine oxide derivatives are presented in Table XV. Corresponding  $J_{CP}$  coupling constants are given in Table XVI. The effect of changes in the oxidation state (PIII to PIV) are given in Table XVII and the



TABLE XV

Carbon-13 Chemical Shifts<sup>a</sup> in P-Phenyl-Phosphorinane and Phosphorinane Oxide Derivatives

Carbon Position	Structure											
	51	51a	15	15a	52	53	53a	54	54a	54b	55	55a
C-2,6												
C-2'6'(a)												
C-2'6'(eq)												
C-3,5												
C-4												
C-q												
C-o												
C-m												
C-p												

<sup>a</sup> Solvent: CDCl<sub>3</sub>.



TABLE XVI

$^{13}\text{C}$ - $^{31}\text{P}$  Nuclear Spin Coupling Constants<sup>a</sup> for P-Phenyl-Phosphorinane and Phosphorinane Oxide Derivatives

Carbon Position	Structure										
	51	51a	15	15a	52	53	53a	54	54a	54b	55b
C-2,6	12.2	65.9	15.9	65.9	89.1	12.6	57.4	19.5	61.0	42.7	61.0
C-2'6'(a)						24.4	37.8	33.0	12.2	24.4	17.1
C-2'6'(eq)						15.9	37.8	13.4	12.2	24.4	4.9
C-3,5	3.7	6.1	0	6.1	6.1	0	0	2.4	0	0	28.1
C-4	0	0	0	7.3	9.8	0	8.5	0	8.5	6.1	11.0
C-9	18.3	89.1	17.1	97.7	6.1 <sup>3</sup> OCH <sub>3</sub>	25.6	81.8	23.2	85.2	66.0	0
C-10	14.6	9.8	14.6	8.5		23.1	8.5	23.2	7.3	8.6	26.9
C-11	4.9	12.2	4.9	12.2		8.5	11.0	9.2	11.0	8.6	23.2
C-12	0	0	0	0		0	0	0	2.3	3.7	8.5
											11.0
											2.4

<sup>a</sup> given in Hertz, sign not determined.

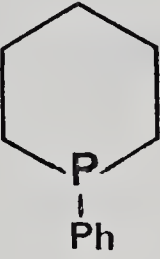
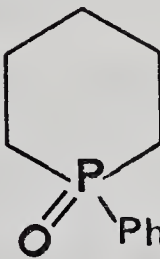
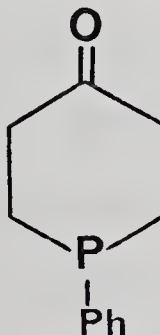
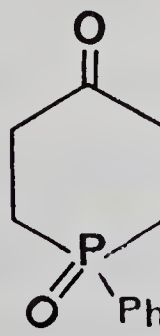






TABLE XVIII

Empirical Tetramethyl Parameters Observed in  
P-Phenyl-Phosphorinane Derivatives

Structure	Parameters				
	$\alpha$	$\beta$	$\gamma(\text{C-4})$	$\gamma(\text{C-q})$	$\delta(\text{C-o})$
	+4.6	+14.1	-7.4	-3.4	+5.7
	+6.0	+17.1	-7.7	+4.5	+2.5
	+11.4	+14.8	+0.8	-1.6	+6.0
	+11.0	+17.4	-0.8	-3.2	+2.2



substituent parameters are presented in Table XVIII.

Assignment of the carbon-13 resonances to the appropriate carbon position in the compounds studied was made using conventional techniques and where ambiguities arose, the magnitude of the  $J_{PC}$  coupling constants enabled identification. Specific assignments are described in the appropriate section.

## C. DISCUSSION

### 1. Phosphorinane Derivatives

#### a. 1-Phenylphosphorinane (51) and 1-Phenyl-4-phosphorinanone (15).

The chemical shifts for the title compounds are average values since there exists an equilibrium between P-phenyl (axial) and P-phenyl (equat.). The reported constant for the conformational equilibrium in solution at 27° for 51 is 0.72<sup>73a</sup>. Hence the axial phenyl configuration is preferred at room temperature. However, the conformational preference, in solution, of the phenyl group in 15 has not been reported. As mentioned earlier the magnitude of the coupling constant  $^2J_{PC}$  between the phosphorus atom and the carbon atoms C-3,5 is related to the position of the conformational equilibrium. Thus, the lack of coupling in 15 indicates the phenyl group prefers an axial orientation, while the value of 3.7 Hz in 51 is in keeping with the conformational equilibrium reported<sup>73a</sup>. The coupling constants to the ortho, meta and para carbons in the phenyl rings of 51 and 15 are identical, 14.6, 4.9 and 0 Hz, respectively, while the C-q coupling is slightly smaller in 15 (17.1 Hz) than 51 (18.3 Hz) suggesting that in the aromatic ring only the  $^1J_{PC}$  coupling constant is sensitive to small



changes in conformational equilibrium. The  $^{13}\text{C}$  evidence suggests the P-phenyl axial configuration in  $\underline{15}$  predominates at room temperature and to a lesser extent in  $\underline{51}$ .

The  $\alpha$ -carbonyl substituent parameter in these molecules is +14.7 ppm. This value is identical to that observed in N-methyl piperidines<sup>43</sup>. It is also apparent that the difference in the substituent at the heteroatom has little effect on the overall chemical shifts. For comparison, the  $^{13}\text{C}$  resonances for the C-3,5 and C-4 carbons in N-methyl (Table VIII) and N-phenylpiperidine (Figure 12, see page No.131) differ only by +0.2 and -0.5 ppm, respectively. Evidently the carbonyl group has similar inductive effects independent of the heteroatom.

#### b. 1-Phenyl-2,2,6,6-tetramethylphosphorinanes

Assignment of the carbon-13 resonances to the appropriate carbons in the tetramethylphosphorinanes was made using conventional techniques. In particular the methylene carbons of the saturated ring in  $\underline{53}$  were assigned on the basis that C-3,5 will experience a deshielding  $\beta$ -effect and C-4 a shielding  $\gamma$ -effect compared to  $\underline{51}$  ( $\beta$  +14.1 ppm,  $\gamma$  -7.4 ppm). For the aromatic carbons in  $\underline{53}$ ,  $\underline{54}$  and  $\underline{55}$  distant dependent  $J_{\text{PC}}$  coupling constants were evident. The para carbons were identified by their lack of coupling to phosphorus, the meta carbons to their insensitivity to substitution effects (chemical shifts remaining constant 127.6 - 128.5 ppm), while the ortho carbons were consistently to low field of the other aromatic carbons. In  $\underline{55}$  proton selective decoupling techniques were used to confirm their assignments. The assignment of the methyl carbons is described below in relation to the conformation of the compounds.



c. Conformational Analysis of 1-Phenyl-2,2,6,6-tetramethyl phosphorinanes.

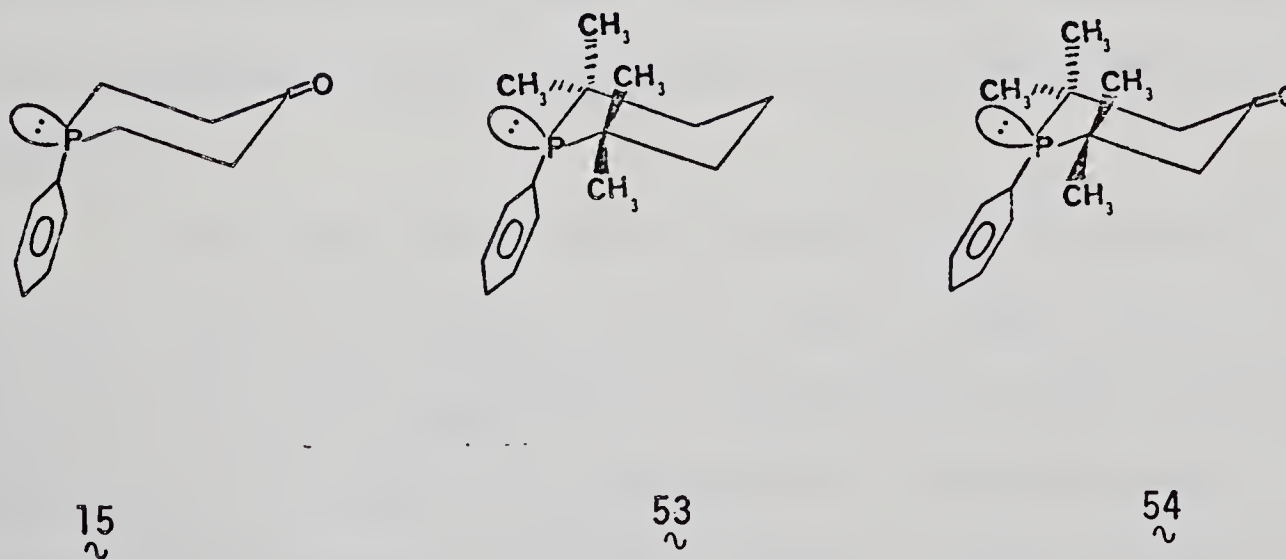
The conformation of the three tetramethyl-phosphorinanes studied may be analyzed using the observed  $^{13}\text{C}$  chemical shifts and the magnitude of the conformationally biased  $^2J_{\text{PC}}$  coupling constant. The methyl carbons in  $53_{\sim}$  and  $54_{\sim}$  are almost magnetically equivalent. The difference in chemical shift between the axial and equatorial groups is 0.5 and 0.9 ppm, respectively. However, in  $55_{\sim}$  there is a definite change either in the ring conformation or the P-phenyl orientations, the methyl resonances differing by 5.8 ppm.

The phosphorinane ring is flattened compared with cyclohexane or other six-membered rings due to the constraints of the phosphorus atom. Thus the deshielding  $\delta$ -effect expected between the axial methyl carbons may be relieved. A concomitant shielding of the equatorial methyl carbons is likely to arise from partial eclipsing of the  $\text{C}_2 - \text{C}_{\text{me}}$  bond with the  $\text{P} - \text{C-q}$  bond, the consequence of distortion of the P-phenyl axial group. The combination of these effects implies that if a conformational equilibrium does exist then the preferred conformation will be that with the pseudo-axial phenyl orientation producing near equivalence of the ring methyl carbons 30.1<sub>0</sub> (ax) 30.6<sub>1</sub> (equat) and 30.9<sub>9</sub> (ax), 30.1<sub>3</sub> (equat) in  $53_{\sim}$  and  $54_{\sim}$ , respectively. On examining the Dreiding models for these molecules the pseudo-axial methyl groups have a smaller dihedral angle relative to the phosphorus lone-pair orbital ( $\sim 0^\circ$ ) compared to the pseudo-equatorial groups ( $>60^\circ$ ). The cis relationship in the former explains the larger coupling constant, 24.4 and 33.0 Hz (compared with 15.9 and 13.4 Hz for the equatorial groups) in  $53_{\sim}$  and  $54_{\sim}$ , respectively. In  $54_{\sim}$  phosphorus



coupling to C-3,5 is observed (2.4 Hz) and can be rationalized by a decrease in the dihedral angle between the phosphorus lone-pair orbital and this carbon position. Furthermore, as indicated by Dreiding models this change in angle would cause a decrease in the dihedral angle to the pseudo-axial methyls and an increase to the pseudo-equatorial methyls. This is evidenced by the phosphorus coupling to the axial and equatorial methyls increasing and decreasing, respectively. Hence the phenyl ring is expected to be tilted away from the phosphorinane ring in  $\underline{54}$  compared to  $\underline{53}$ . The pseudo-equatorial methyls in  $\underline{54}$  are shielded (30.1<sub>3</sub> ppm) with respect to the pseudo-axial methyls (30.9<sub>9</sub> ppm) due to a greater eclipsing of the C<sub>2</sub> - C<sub>me</sub> and P - C<sub>q</sub> bonds and a greater separation of the 1,3-diaxial methyl groups.

These results suggest that changes in conformation in phosphorinane ring systems can be better followed by changes in the carbon-phosphorus coupling constants. The preferred conformations of  $\underline{15}$ ,  $\underline{53}$  and  $\underline{54}$  are shown below.



The alcohol derivative  $\underline{55}$  (of  $\underline{54}$ ) was obtained by a lithium aluminum hydride reduction. The hydride ion ( $H^{\ominus}$ ) presumably attacks



from the less hindered side (Figure 10a) resulting in an axial hydroxyl group<sup>118</sup> (Figure 10b) which would produce severe 1,3-diaxial interactions with the pseudo-axial C-2'6' methyls in the chair conformation. A more favourable conformer (Figure 10c) with the phenyl group equatorially orientated results from chair-to-chair interconversion. The structure of 55 (Figure 10c) is verified since large  $^2J_{PC}$  coupling to C-3,5 (11.0 Hz) is observed implying an equatorial phosphorus substituent (vide supra). Further, large differences in the chemical shifts of the methyl groups and their coupling to phosphorus are observed 26.4<sub>9</sub> (4.9 Hz) and 32.3<sub>4</sub> ppm (28.1 Hz). These values characterize the axial and equatorial methyl groups, respectively. Examination of Dreiding models indicates that the phosphorus lone pair orbital and axial methyl carbons are trans to each other with a dihedral angle close to 180°, while a cis-relationship is evident in the case of the equatorial methyls. The fact that the couplings to the C-3,5 and C-2',6' (equat) carbons are different (11.0 and 28.1 Hz, respectively) indicates that the dihedral angle is smaller between the phosphorus lone pair and the C-2'6' equatorial methyl groups presumably the consequence of the phenyl group tilting towards the axial orientation.

As the phenyl group becomes progressively more equatorial in 53, 54 to 55 the C-q carbon resonance moves to higher field, 137.4<sub>2</sub>, 135.8<sub>6</sub> and 133.3<sub>9</sub> ppm, respectively. The possibility that the differing orientations of the methyl groups contribute to increased steric effects at the C-q carbon cannot be ruled out. However, similar shielding was observed in the equatorial phenyl isomer of 1-phenyl-3,5-dimethyl-4-phosphorinanone (vide-infra).



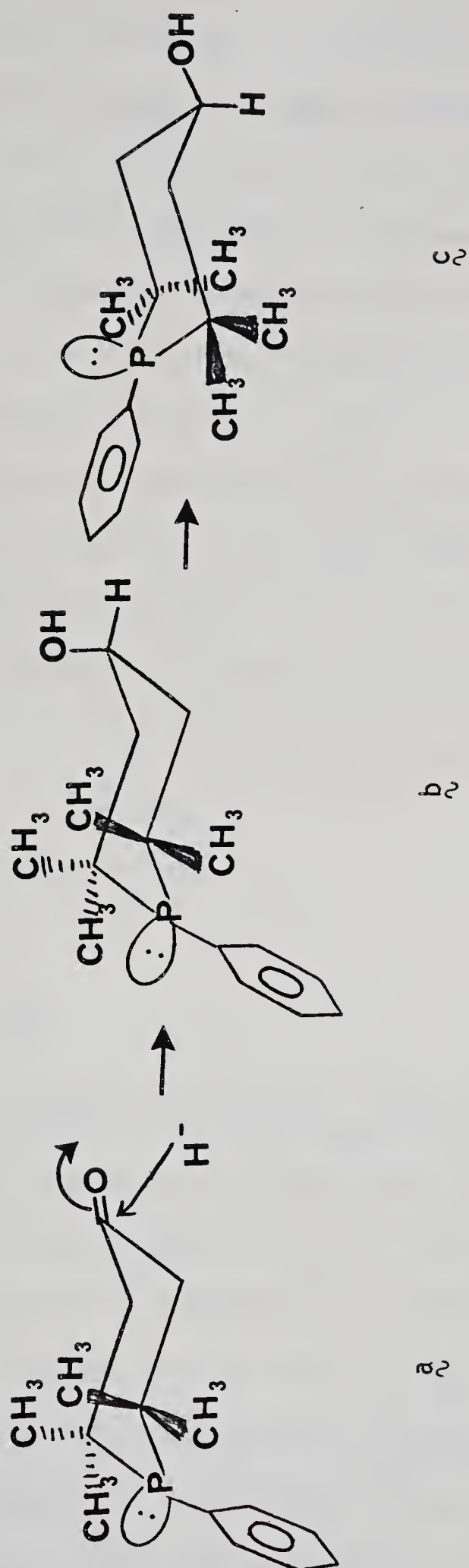
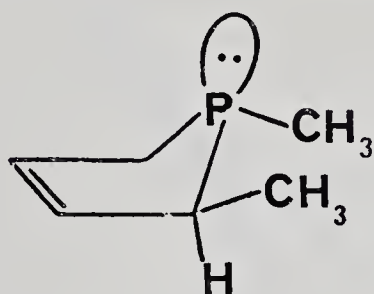


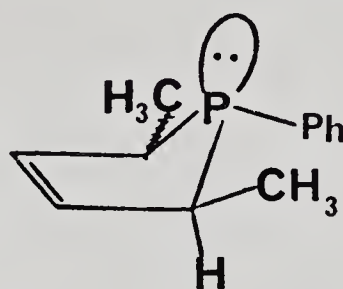
FIGURE 10: Lithium aluminum hydride reduction of 1-phenyl-2,2,6,6,6-pentamethylcyclohexanone.



Consideration of the  $^2J_{PC}$  coupling values in  $\underset{\sim}{53}$ ,  $\underset{\sim}{54}$  and  $\underset{\sim}{55}$  together with those in cis- and trans-1-methyl-4-*t*-butyl-4-phosphorinanol<sup>74</sup> suggests that the  $^2J_{PC}$  coupling has a maximum value ( $\sim 33$  Hz) when the dihedral angle approaches  $0^\circ$  ( $\underset{\sim}{53}$ ) and decreases to about 7 Hz at  $60^\circ$  (cis-1,4-disubstituted phosphorinanol) and to 0 Hz at  $180^\circ$  ( $\underset{\sim}{15}$ ,  $\underset{\sim}{53}$  and trans-1,4-di-substituted phosphorinanol). A graph of these results is presented in Figure 11. Further examples of an approximate  $0^\circ$  dihedral angle corresponding to a  $^2J_{PC}$  coupling of 33 Hz have been reported in the literature<sup>79</sup>. The trans-isomers of 1,2-dimethyl- $\Delta^3$ -phospholene ( $\underset{\sim}{56}$ ) and 2,5-dimethyl-1-phenyl- $\Delta^3$ -phospholene ( $\underset{\sim}{57}$ ) have  $^2J_{PC}$  coupling constants to the ring methyls of 32 and 30 Hz, respectively.



$\underset{\sim}{56}$



$\underset{\sim}{57}$

#### d. $^1H$ Chemical Shift and $J_{PH}$ Coupling

The pmr results for the 1-phenyl-2,2,6,6-tetramethyl-phosphorinanes are presented in Table XIX. The axial methyls are assigned to the low field resonance to provide consistency with the proton-selective decoupling experiments for  $\underset{\sim}{55}$ . I.e. irradiation of the low field methyl proton resonance (1.28 ppm) produced enhancement of the carbon resonance at high field assigned to the axial methyl carbon on the basis of the  $\gamma$ -effect experienced at this site. The proton data show the pseudo-axial methyl proton chemical shifts remain constant while the equatorial methyl proton shifts move progressively



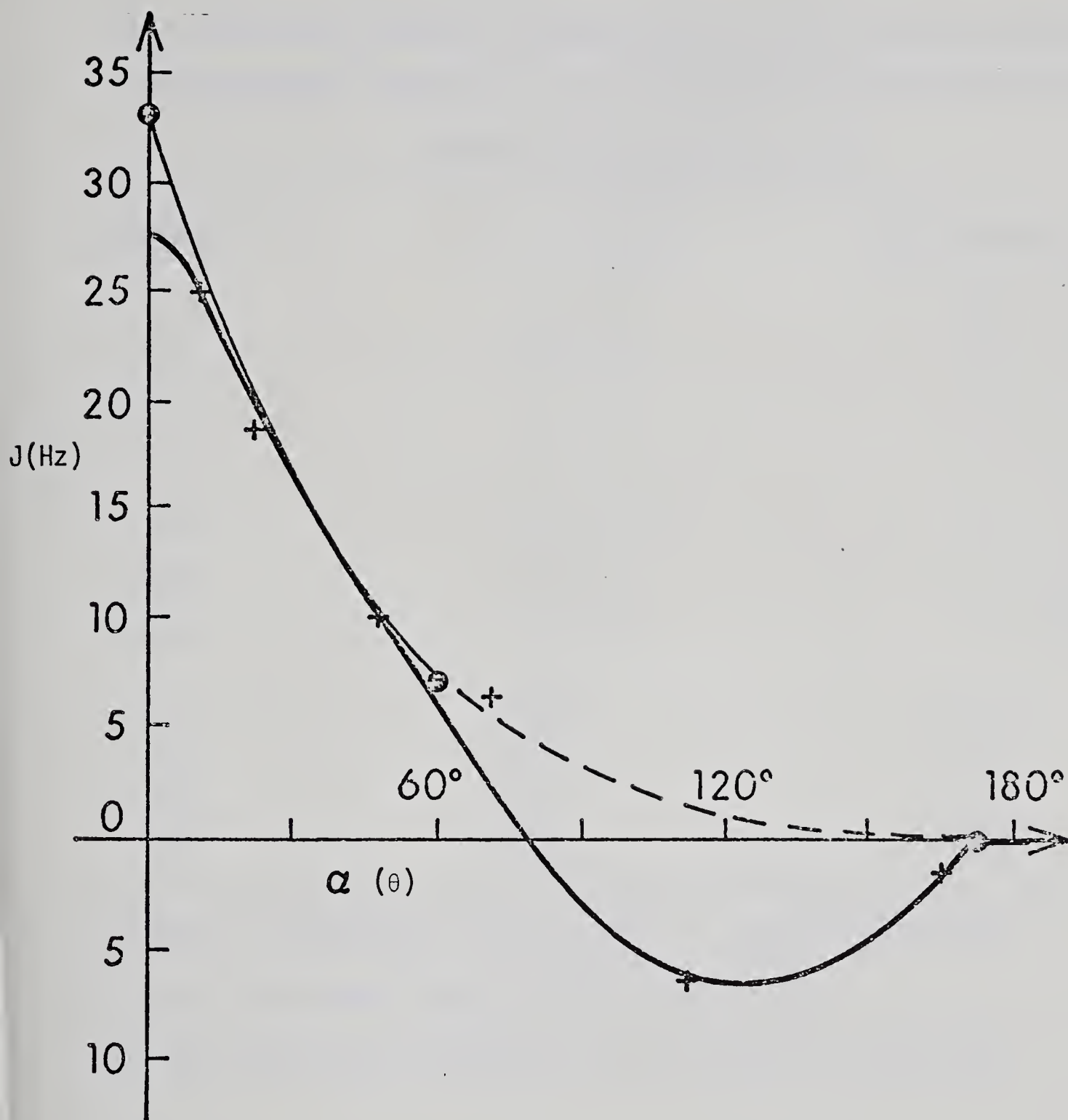


FIGURE 11: A Karplus relationship between the  ${}^2J_{PH}$  coupling constant and dihedral angle ( $\theta$ ) (—)<sup>63b</sup> and the  ${}^2J_{PC}$  coupling constant and dihedral angle (—, ---). Since the sign of the coupling constants was not determined the position of the dotted line could indicate positive or negative coupling values.



TABLE XIX

$^3J_{P-H}$  Coupling Constants<sup>a</sup>, Proton Chemical Shift<sup>b</sup> and Shift Differences<sup>c</sup>  
for the Methyl Protons in 2,2,6,6-Tetramethylphosphorinane, Phosphine  
and Phosphine Oxide Derivatives

<u>Compound</u>	<u>C-2'6' axial Me</u>	<u>C-2'6' equatorial Me</u>
53 <sub>~</sub>	1.2 <sub>8</sub> (19)	0.8 <sub>1</sub> (10)
54 <sub>~</sub>	1.3 <sub>1</sub> (18)	0.9 <sub>5</sub> (11)
55 <sub>~</sub>	1.2 <sub>8</sub> ( 8)	1.0 <sub>8</sub> (23)
53a <sub>~</sub>	1.3 <sub>0</sub> (12.5)	1.0 <sub>1</sub> (14)
54a <sub>~</sub>	1.3 <sub>5</sub> (5)	1.1 <sub>3</sub> (6.5)
55a <sub>~</sub>	1.5 <sub>0</sub> (12)	1.1 <sub>2</sub> (12)
53a <sub>~</sub>	+0.0 <sub>2</sub> <sup>c</sup>	+0.2 <sub>0</sub> <sup>c</sup>
54a <sub>~</sub>	+0.0 <sub>4</sub>	+0.1 <sub>8</sub>
55a <sub>~</sub>	+0.2 <sub>2</sub>	+0.0 <sub>4</sub>

<sup>a</sup> Values in parenthesis given in Hertz. Signs not determined.

<sup>b</sup> Given in ppm downfield from TMS, solvent CDCl<sub>3</sub>.

<sup>c</sup> Given in ppm, plus indicates oxide derivative to low field.



( $\underset{\sim}{53} \rightarrow \underset{\sim}{55}$ ) to lower field with a concomitant increase in the  $^3J_{PH}$  coupling constant. This is expected since any change in the orientation of the phenyl group towards equatorial will affect the equatorial methyl group, the methyl protons being in the deshielding zone of the phenyl ring. The magnitude of the  $^3J_{PH}$  coupling is known to have a geometrical dependence<sup>119</sup> similar to that described for the  $^2J_{PC}$  values. Thus, the increase in  $^3J_{PH}$  couplings is consistent with the changes in phenyl group orientation previously suggested. The larger coupling (19 Hz) to the low field C-2'6' methyl protons in  $\underset{\sim}{53}$  and  $\underset{\sim}{54}$  compared to the high field methyl protons (11 Hz) substantiates the assignment to the pseudo-axial and equatorial methyl groups, respectively. The phenyl group is in the axial orientation. Analogous values are reported<sup>119</sup> for the  $^3J_{PH}$  couplings to the C-2' methyl protons in the cis- and trans-isomers of  $\underset{\sim}{56}$  (P-CH<sub>3</sub> or P-Ph) 10 Hz and 18 Hz, respectively, indicating similar geometric relationship between the methyl groups and phosphorus lone pair orbital in these isomers.

In  $\underset{\sim}{53}$  and  $\underset{\sim}{54}$  the methyl proton chemical shifts and  $^3J_{PH}$  coupling constants are less sensitive to the conformational change than the analogous carbon-13 data. However, the change to a chair conformation with an equatorial phenyl group as in  $\underset{\sim}{55}$  is also indicated by the proton data. The axial methyl protons at 1.28 ppm have a small  $^3J_{PH}$  coupling constant of 8 Hz, while the equatorial methyl protons resonate at lower field (1.08 ppm) with a significantly larger coupling (23 Hz). These results are consistent with the size of the dihedral angle between the phosphorus lone pair orbital and the respective methyl group. In  $\underset{\sim}{53}$  and  $\underset{\sim}{54}$  the corresponding couplings to the equatorial methyl protons are 10 and 11 Hz, respectively.



e.  $^{13}\text{C}$  Additivity Relationships

Due to a difference in the conformations of the three tetramethylphosphorinanes  $\underset{\sim}{53}$ ,  $\underset{\sim}{54}$  and  $\underset{\sim}{55}$  discussion of additivity effects of the carbonyl and hydroxyl group is not valid. However, the effects of tetramethyl substitution in the phosphorinanes  $\underset{\sim}{51}$  and  $\underset{\sim}{15}$  can be discussed.

The shifts induced at C-3,5 ( $\beta$ -effect) on substitution of the geminal methyl groups at C-2 and C-6 are similar, +14.1 and +14.8 in  $\underset{\sim}{53}$  and  $\underset{\sim}{54}$ , respectively. The  $\alpha$ -effect is attenuated in  $\underset{\sim}{51}$  (+4.6 ppm) and  $\underset{\sim}{15}$  (+11.4 ppm) confirming the suggestion that a conformational difference exists between these molecules. A  $\gamma$ -gauche shielding effect is observed at C-4 (-7.4 ppm) in  $\underset{\sim}{51}$ , while in  $\underset{\sim}{15}$  the removal of the C-4 proton greatly attenuates this effect (+0.8 ppm). A  $\gamma$ -effect is also observed at C-q in the phenyl group, the largest effect being in  $\underset{\sim}{51}$  (-3.4 ppm). A large  $\delta$ -deshielding effect is found at the ortho carbons (+5.7 and +6.0 ppm in  $\underset{\sim}{51}$  and  $\underset{\sim}{15}$ , respectively) and probably arises from sym-axial interactions. These data are summarized in Table XVIII.



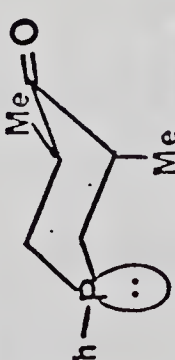
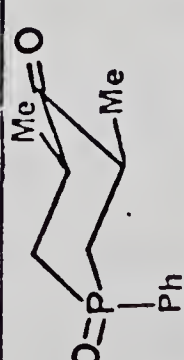
f. 1-Phenyl-3,5-dimethyl-4-phosphorinanone ( $\underset{\sim}{58}$ )

Evidence for three major isomeric products of 1-phenyl-3,5-dimethyl-4-phosphorinanone ( $\underset{\sim}{58}$ ) in the crude reaction product arising from the condensation of phenylphosphine and 2,4-dimethyl-1,4-pentadien-3-one was indicated by the observation of three carbonyl resonances at 212.3, 213.2 and 214.5 ppm in the carbon-13 nmr spectrum. The carbon-13 chemical shifts for the three isomers and the major phosphine oxide derivative are presented in Table XX. The presence of three isomers was also indicated in the pmr spectrum which exhibited



TABLE XX

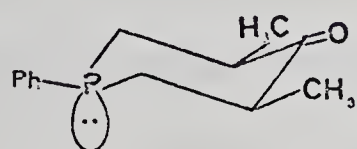
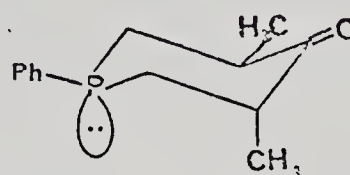
Carbon-13 Chemical Shifts<sup>a</sup> of 1-Phenyl-3,5-Dimethyl-4-Phosphorinanone Isomers and Major P-oxide Isomer

Structure	Carbon Position									
	C2	C3	C4	C5	C6	C3'	C5'	C-g		
 58α	34.0 <sub>1</sub>	41.9 <sub>2</sub>	213.2 <sub>5</sub>	41.9 <sub>2</sub>	34.0 <sub>1</sub>	16.7 <sub>8</sub>	16.7 <sub>8</sub>	137.6 <sup>b</sup>		
	15.9	0	0	0	15.9	0	0	16.0		
 58β	36.1 <sub>7</sub>	43.2 <sub>4</sub>	212.2 <sub>8</sub>	43.2 <sub>4</sub>	36.1 <sub>7</sub>	17.4 <sub>8</sub>	17.4 <sub>8</sub>	131.8 <sup>b</sup>		
	11.0	8.6	0	8.6	11.0	0	0	21.9		
 58γ	29.0	41.4	214.3	39.0	29.6	16.6	18.0	- <sup>d</sup>		
	15.9	10.9	0	4.9	13.4	0	0	-		
 58αα	37.6 <sub>8</sub>	40.1 <sub>9</sub>	210.8 <sub>2</sub>	40.1 <sub>9</sub>	37.6 <sub>8</sub>	16.5 <sub>9</sub>	16.5 <sub>9</sub>	131.2 <sub>5</sub>	130.2 <sub>8</sub>	132.2 <sub>8</sub>
	64.7	4.9	4.9	4.9	64.7	13.4	13.4	100.1	9.8	12.2 <sup>c</sup>

<sup>a</sup> Solvent CDCl<sub>3</sub>.<sup>b</sup> Only C-q chemical shifts obtainable due to overlapped of o, m and p resonances.<sup>c</sup> Broad resonance.<sup>d</sup> Concentration of isomer too small to obtain chemical shift.



five methyl resonances having similar chemical shifts and coupling constants to those reported by Katritsky and co-workers<sup>120</sup> for the product obtained from cyclization of bis-(2-methoxycarbonylpropyl)-phenylphosphine in their attempts to prepare the title compound  $58_{\sim}$ , i.e.,  $0.9_8$  (6.4 Hz),  $1.0_8$  (6.5 Hz) and  $1.2_4$  ppm. The doublets were assigned to the major isomers  $58_{\sim\beta}$  and  $58_{\sim\alpha}$ , respectively, and the resonance at  $1.2_4$  ppm to the trans-isomer  $58_{\sim\gamma}$ . Other methyl resonances were obscured.

 $58_{\sim\beta}$  $58_{\sim\alpha}$  $58_{\sim\gamma}$ 

Column chromatography on alumina separated the isomers  $58_{\sim\alpha}$  and  $58_{\sim\beta}$  from  $58_{\sim\gamma}$ . Furthermore, the relative concentrations of the isomers  $58_{\sim\alpha}$  and  $58_{\sim\beta}$  differed before and after chromatography. The isomer,  $58_{\sim\beta}$  predominated in the original mixture while the isomer,  $58_{\sim\alpha}$  dominated after chromatography. Further separation could not be achieved using these techniques. The mixtures were, therefore, studied and carbon-13 nmr data was abstracted by difference measurements.

The absence of phosphorus coupling to the carbons C-3,5 in  $58_{\sim\alpha}$  identifies the axial orientation of the phenyl group. In contrast, the  $^2J_{PC}$  coupling constant 8.6 Hz is observed in  $58_{\sim\beta}$  characterizing the equatorial orientation of the phenyl group. A steric  $\gamma$ -effect of -1.4



ppm is observed at C-3,5 in  $58\alpha$ . Comparison of the data for  $58\alpha$  and  $15$  enables derivation of the equatorial methyl parameters ( $\alpha$ , +3.7 and  $\beta$ , +10.2 ppm) which are 1 ppm greater than those in the analogous N-methylpiperidine. (Chapter II, Table II,  $\alpha$  +2.8 and  $\beta$  +9.1 ppm). Comparison of  $58\beta$  and  $58\alpha$  now enables the derivation of the parameters for the change in orientation of the phenyl group. These values are  $\alpha$ , -2.2;  $\beta$ , -1.3 and  $\gamma$ , +0.9 ppm. The C-q carbon shift (137.6 ppm) in  $58\alpha$  is identical to that in  $15$ . In  $58\beta$  where the phenyl group is established as equatorial the C-q chemical shift is to high field (131.8 ppm). This upfield shift is the reverse of that observed in the axial compared to equatorial orientated 4-phenyl substituent in nitrogen heterocycles<sup>55,56</sup>. However, the concomitant shift at C-3,5 for this change in orientation (-1.3 ppm) was observed. It seems probable that the P-Ph bond contributes to the reversed effect.

The absence of symmetry in the isomer,  $58\gamma$ , is shown by the presence of distinct resonances for each ring carbon atom. The  $\beta$ -effect of an axial compared to an equatorial methyl suggests that C-2 (29.0 ppm) should be to high field of C-6 (29.6 ppm). The expected  $\gamma$ -effect of the C-3' methyl group at C-5 suggests the resonance at 39.0 ppm be assigned to C-5 and that at 41.4 ppm to C-3. The equatorial methyl group C-5' (18.0 ppm) was assigned by comparison with the similar methyl in  $58\beta$  (17.5 ppm). The axial methyl group C-3' is thus to high field (16.6 ppm).

The phosphorus coupling to the carbons C-2,6 is larger in  $58\alpha$  than  $58\beta$  (15.9 and 11.0 Hz, respectively) a feature also observed in 1-methyl-4-phosphorinanol<sup>74</sup> where  $^1J_{PC}$  coupling is larger when the P-substituent is axial. However, an opposite result is obtained for the



coupling to C-q, while the methyl in the phosphorinaneols has a larger coupling when axially oriented. It is clear that discussion relating steric effects and  $^1J_{PC}$  couplings must consider similarly hybridized carbon atoms. In our case the axially oriented  $sp^2$  hybridized benzene carbon induces smaller couplings than a corresponding  $sp^3$ -methyl carbon.

## 2. Phosphorinane Oxide Derivatives

The carbon resonances of the phosphorinane oxides were assigned using conventional techniques, in particular, proton selective decoupling. For 1-methoxy-1-phenyl-4-phosphorinanone  $\underline{52}$ , C-2,6 was distinguished from C-3,5 by its larger  $J_{PC}$  coupling constant. Significant changes accompany conversion to the oxide: 1) the oxygen atom exerts characteristic  $\alpha$ -,  $\beta$ - and  $\gamma$ -effects, 2) the electron density on phosphorus is diminished compared with the phosphine, 3) changes in bond angle and bond lengths occur, and 4) anisotropic effects may differ between phosphines and their oxides. The carbon-13 chemical shift of the oxides are presented in Table XV and the corresponding  $J_{PC}$  coupling constants in Table XVI.

### a. (i) Conformational and Additivity Effects

It is known that peroxide oxidation of phosphines is accompanied by retention of configuration<sup>121</sup>. Hence the basic conformations of the cyclic phosphines established earlier should be retained.

The average  $\beta$ -effect of the oxygen at C-2,6 in  $\underline{51a}$ ,  $\underline{15a}$  and  $\underline{58\alpha a}$  compared to their corresponding phosphines is +3.5 ppm, while in the tetramethyl derivatives the effect varies with conformation from



+2.8 ppm in  $54a$  to +5.2 ppm in  $51a$ . In  $55a$  the  $\beta$ -effect is +3.0 ppm. It is noteworthy that while the  $\beta$ -effect at C-2,6 is deshielding, a large shielding effect occurs at the corresponding site, C-q (-5.8  $\rightarrow$  -8.3 ppm). An explanation follows (section b). Of greater significance is the  $\gamma$ -effect of the oxygen which is expected to be similar to that in sulphide derivatives<sup>73</sup>. Shielding effects (-1.5, -2.0 and -1.7 ppm) are observed at C-3,5 in  $51a$ ,  $15a$  and  $58\alpha a$ , respectively, which correspond with similar effects reported for the 1-methyl and 1-phenylphosphorinane sulphides<sup>73a</sup>, -1.0 and -1.6 ppm, respectively. This shielding was taken as evidence for the sulphur atom being largely in an axial orientation<sup>73</sup>. However, this is probably not the case in the oxides. We have observed that in both phosphine oxide isomers of 8-phenyl-8-oxo-8-phosphobicyclo-[3.2.1]octan-3-one the  $\gamma$ -effect is shielding (vide-infra). Further the corresponding chair conformer of  $58\alpha a$  with an axial oxygen atom is unlikely to contribute due to severe 1,3-diaxial interactions. The aromatic carbon atoms shifts in  $58\alpha a$  and  $15a$  are also identical which suggest that the same conformation holds for both molecules. It appears, that in the phosphorinanes, the  $\gamma$ -effect due to phosphine oxide oxygen is upfield in both axial and equatorial orientations of the oxygen with the larger effect in the former.

Consideration of the chemical shifts of  $15a$  and  $52$ , in particular, the similar shielding at C-3,5, 36.2<sub>8</sub> and 36.8<sub>7</sub> ppm, suggests similar conformations for these compounds. The shielding effect (-3.3 ppm) at C-2,6 in these systems is indicative of the difference in the inductive effects of the phenyl and methoxy groups.

The conformation of the tetramethyl phosphine oxide derivatives should be approximately the same as the parent phosphine. The axial



oxygen atom in  $55a$  does cause the expected  $\gamma$ -shielding effects at C-3,5 (-3.8 ppm), at C-o (-3.7 ppm) and C-2',6' (equat) (-6.8 ppm) (Table XVII). The latter data reinforces the assignment of these carbon atoms since the C-2',6' (axial) methyl groups are only slightly shielded (-1.0 ppm) relative to those in the phosphine and the meta carbons are not affected (+0.2 ppm) on oxidation.

The carbon and proton chemical shifts are consistent. On oxidation the methyl proton resonances are deshielded (Table XIX) while the carbon resonances are shielded (Table XVII). In particular in  $55a$  the equatorial methyl carbon is shielded (-6.8 ppm) to a larger extent than the axial (-1.0 ppm) while the proton shift differences (Table XIX) are +0.2<sub>2</sub> and +0.0<sub>4</sub> ppm, respectively.

The  $\beta$ -oxygen substitution effects in  $53a$  and  $54a$  (-8.3 and -7.7 ppm, respectively) are different than in  $55a$  (-5.8 ppm). This is probably due to the change in phenyl group conformation, from pseudo-axial in the former to equatorial in the latter. The  $\gamma$ -oxidation effect on the C-2',6' methyl carbons (axial and equatorial) are approximately the same in  $53a$  (-5.1 and -5.6 ppm, respectively) suggesting a similar orientation of these methyl groups about the phosphine oxide bond. While in  $54a$  and effect differs, (-5.6 and -4.7 ppm, for axial and equatorial methyls, respectively). This is consistent with the change in orientation of the phenyl group in going from  $53a$  to  $54a$ . In the latter, the greater  $\gamma$ -effect on the axial methyl compared to the equatorial is attributable to further eclipsing of the P-O and C-Me<sub>(ax)</sub> bonds than the P-O and C-Me<sub>(equat)</sub> bonds.

Oxidation of tetramethylphosphorinanes gives a shielding  $\delta$ -effect at C-4 (-1.4, -4.4 and -1.9 ppm for  $53a$ ,  $54a$  and  $55a$ ,



respectively). The increase in value is associated with the presence of the carbonyl group. A similar observation was made for the less substituted derivatives (-1.1, -2.8 and -2.4 ppm in  $\underline{51a}$ ,  $\underline{15a}$  and  $\underline{58\alpha a}$ , respectively). Generation of the sulphide ( $\underline{54b}$ ) gives similar shielding parameters to those in the oxide ( $\underline{54a}$ ) (Table XVII), with the exception of the  $\beta$ -effect, which is larger in the sulphide (+4.6 ppm).

#### a. (ii) P-atom Hybridization

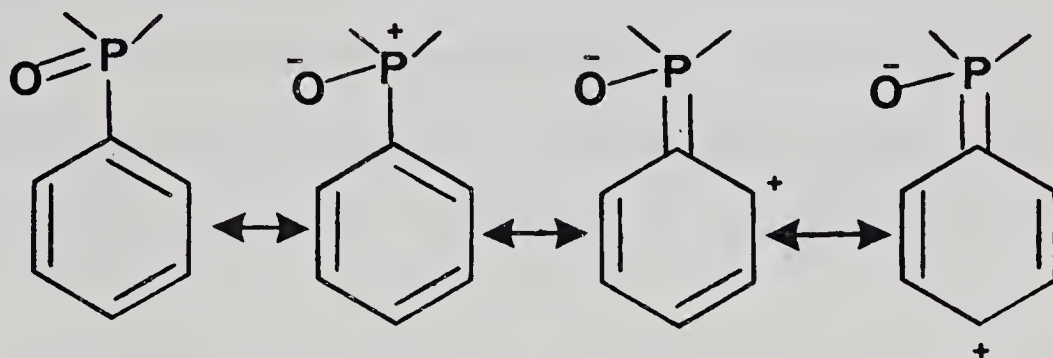
Changes in the oxidation state of phosphorus from PIII to PIV, result in rehybridization of the atomic orbitals of phosphorus. The amount of s-character is increased in PIV compounds and hence a large increase is observed in the  $^1J_{PC}$  coupling constants (50 Hz in the molecules studied). Of particular interest is the long range  $^3J_{PC}$  coupling constant which is larger than  $^2J_{PC}$  in both the saturated and aromatic rings. A similar observation was made in the triphenylphosphorus ylides<sup>122</sup> although no explanation was offered. The long range coupling constants were used to confirm the aromatic ring carbon atom assignments ( $^3J_{PC\underline{m}} > ^2J_{PC\underline{o}}$ )

#### b. The Phosphorus-Oxygen Bond

The amount of  $\pi$ -bonding in the P-O bond of phosphine oxides is of theoretical interest and has been the source of much controversy<sup>82,123,124</sup>. Comparison of the  $^{13}C$  chemical shifts of the C-p carbon in the phosphine and phosphine oxides in the series of compounds studied (Table XVII) reveals a large deshielding effect on formation of the oxide. Values range from +4.4 ppm in  $\underline{51}$  and  $\underline{15}$  to +2.0 ppm in tetramethyl derivatives. These large shift differences



(an  $\epsilon$ -effect) are not attributable to an inductive effect but rather a resonance effect. Delocalization of the aromatic  $\pi$ -electrons towards phosphorus, decreases the electron density at C-p, therefore deshielding this position. The results imply the P-O bond is polarized  $\overset{+}{\text{P}}-\overset{-}{\text{O}}$  and present to a significant amount. The resonance forms possible are:



A similar deshielding effect is not observed at C-o since upon oxidation there is a concomitant large shielding  $\gamma$ -effect at this position. A similar  $\epsilon$ -deshielding effect (+2.0 ppm) is also present in the sulphide derivative  $54b$  and one must conclude that the P-S bond is also polarized. In more polar solvents the contribution of the polar form is expected to be enhanced.

Another phenomenon resulting from oxide formation is the large shielding effect on the quaternary carbon, C-q (average -7.1 ppm, not including  $55a$ ). This observation presumably arises from electronegativity differences between the carbon and phosphorus atoms, the phosphine oxide bond inducing a build-up of electron density on the quaternary carbon centre.

### 3. Mono-, Di-, and Triphenylphosphine and their Oxides

While several authors have reported the  $^{13}\text{C}$  chemical shifts and coupling constants for triphenylphosphine<sup>71,76,77,125</sup>, similar results for the other aryl phosphines and their oxides have not been



previously reported. In order to generalize on the observations concerning oxidation of phosphorus discussed above we have studied the carbon-13 spectra of the series, phenyl, diphenyl and triphenylphosphine and their corresponding oxides. The data is presented in Table XXI.

The assignment of the carbon resonances to the appropriate position was aided by comparison with the chemical shifts in the phosphorinanes. Modulated off-resonance spectra identified the quaternary carbons and the distant dependant  $J_{PC}$  coupling constants was used to differentiate the C-o and C-m carbons in the phosphine and phosphine oxide.

The chemical shifts of the phosphines were determined in both  $CDCl_3$  and  $MeOH_{d-4}$ . In these solvents the carbons, C-o, C-m and C-p undergo only minor solvent shifts while the C-q carbon shifts to lower field with increase in phenyl substitution. That is, the  $\beta$ -effect is attenuated. For example, from +6.6 ppm in diphenylphosphine to +1.7 ppm in triphenylphosphine. The absence of change in the chemical shifts of the ortho-, meta- and para-carbons indicates that there is no change in involvement of the phosphorus lone-pair orbital in delocalization into the aromatic ring. It is generally accepted that the electron donating character of the phosphorus atom in arylphosphines is very weak<sup>123</sup>. However on oxidation the increased positive character of the phosphorus atom should confer on itself a higher electron withdrawing character. The  $^{13}C$  chemical shifts of the C-p carbons do indeed exhibit a larger deshielding effect (+4.6 ppm) indicative of the resonance effects discussed earlier. The ortho position is shielded ( $\gamma$ -effect) with the shift to high field becoming greater in the less substituted phosphine. Oxidation of triphenylphosphine (59) exhibits a



TABLE XXI

$^{13}\text{C}$  Chemical Shift<sup>a</sup>,  $J_{\text{PC}}$  Coupling Constants<sup>b</sup> and Oxide Additivity Parameters<sup>c</sup> in Mono-, Di- and Triphenyl-  
phosphine and their Oxides

Carbon Position	$^{13}\text{C}$ -Chemical Shifts <sup>a</sup>									
	$59_{\sim}$ $\phi_3\text{P}^{\Delta}$	$59_{\sim}$ $\phi_3\text{P}^{\square}$	$60_{\sim}$ $\phi_2\text{PH}^{\Delta}$	$60_{\sim}$ $\phi_2\text{PH}^{\square}$	$61_{\sim}$ $\phi\text{PH}_2^{\Delta}$	$61_{\sim}$ $\phi\text{PH}_2^{\square}$	Structure $59_{\sim}$	$60_{\sim}$	$61_{\sim}$	$61_{\text{a}}$
C-q	137.3 <sub>5</sub>	139.0	134.6 <sub>2</sub>	135.4 <sub>3</sub>	128.0 <sub>1</sub>	128.9 <sub>8</sub>	$\phi_3\text{P}(\text{O})^{\Delta}$	134.5 <sub>1</sub>	128.2 <sub>0</sub>	130.5 <sub>8</sub>
C-o	133.7 <sub>9</sub>	134.7 <sub>3</sub>	133.9 <sub>2</sub>	134.4 <sub>3</sub>	134.5 <sub>7</sub>	135.4 <sub>3</sub>	$\phi_3\text{P}(\text{O})^{\Delta}$	132.6 <sub>5</sub>	130.7 <sub>7</sub>	134.2 <sub>7</sub>
C-m	128.5 <sub>0</sub>	129.6 <sub>3</sub>	128.4 <sub>7</sub>	129.0 <sub>9</sub>	128.0 <sub>1</sub>	128.9 <sub>8</sub>	$\phi_3\text{P}(\text{O})^{\Delta}$	129.6 <sub>3</sub>	128.6 <sub>3</sub>	131.5 <sub>9</sub>
C-p	128.6 <sub>6</sub>	129.8 <sub>5</sub>	128.3 <sub>4</sub>	128.9 <sub>3</sub>	128.3 <sub>9</sub>	129.3 <sub>6</sub>	$\phi_3\text{P}(\text{O})^{\Delta}$	133.3 <sub>0</sub>	132.8 <sub>1</sub>	130.3 <sub>2</sub>
$J_{\text{PC}}$ Coupling Constants <sup>b</sup>										
C-q	12.2	25.6	15.9	11.0	4.9	4.9	108.6	137.9	15.9	47.6
C-o	19.5	20.8	15.9	17.0	15.9	15.9	9.8	11.0	12.2	17.1
C-m	7.3	9.8	6.1	7.3	4.9	4.9	12.2	12.2	13.4	22.0
C-p	0	0	0	0	0	0	0	broad	2.4	6.1



TABLE XXI (cont'd)

$^{13}\text{C}$  Chemical Shift,  $J_{\text{PC}}$  Coupling Constants<sup>b</sup> and Oxide Additivity Parameters<sup>c</sup> in Mono-, Di- and Triphenyl-

phosphine and their Oxides

	Oxide Additivity Parameters <sup>c</sup>			
	$\phi_3\text{P}$	$\phi_2\text{PH}$	$\phi\text{PH}_2(\text{CDCl}_3)$	$\phi\text{PH}_2(\text{MeOH}_{\text{d-4}})$
C-q	-5.0	-0.1	+0.2	+1.6
C-o	-1.2	-1.7	-3.8	-1.2
C-m	+1.1	+1.2	+0.6	+2.6
C-p	+4.6	+4.8	+4.4	+1.0

<sup>a</sup> Solvent  $\text{CDCl}_3$ ,  $\text{MeOH}_{\text{d-4}}$ ,  $\phi_3\text{P}(\text{O})$  and  $\phi_2\text{P}(\text{O})\text{H}$  insoluble in  $\text{MeOH}$ .

<sup>b</sup> Given in Hertz, signs not determined.

<sup>c</sup> Given in ppm, negative sign indicates oxide to high field.



shielding effect (-5.0 ppm) at C-q similar in magnitude to that in the phosphorinanes but oxidation of 60 and 61 causes practically no change in the chemical shift of the quaternary carbon. This attenuated effect in the latter may be attributed to an increase in the deshielding  $\beta$ -effect at C-q compensating for any shielding effects imparted by the phosphine oxide bond.

A solvent effect is apparent in the phosphine chemical shifts. The carbon chemical shifts move to lower field in methanol as a consequence of hydrogen bonding of the phosphorus lone-pair with the solvent. This is more noticeable in phenylphosphine oxide (61a). The resonance effect is attenuated as exhibited by the C-p carbon being deshielded (+1.0 ppm) compared to +4.4 ppm in deuteriochloroform. The difference in the oxide additivity parameters determined for solutions in  $\text{CDCl}_3$  and  $\text{CD}_3\text{OD}$  is possibly due to the latter solvent enhancing the dipolar form of the phosphorus-oxygen bond by hydrogen bonding to the P and O atoms. No structural changes were produced by the  $\text{methanol}_{\text{d-4}}$ . On changing the solvent back to deuteriochloroform the original spectrum was obtained. All other oxides are insoluble in methanol.

The cmr results thus provide evidence of the lack of phosphorus lone-pair electron involvement in delocalization in the phenylphosphines and a significant electron withdrawal effect in the corresponding oxides. The dipolar form of the phosphorus-oxygen bond is enhanced in protic solvents.

#### 4. The 8-Phosphabicyclo[3.2.1]octan-3-one System

The  $^{13}\text{C}$  chemical shifts and coupling constants for the parent compound 62, its methiodide derivative 63, and the two oxide isomers



$62_a$  and  $62_b$  are given in Table XXII. The carbon resonances were assigned by use of conventional techniques, in particular, in  $62$ , C-6,7 was distinguished from C-2,4 by proton selective-decoupling, in  $63$  by a typical  $\gamma$ -effect at C-2,4 and in  $62_a$  and  $62_b$  by comparison of the axial and equatorial oxide  $\gamma$ -effects discussed earlier. C-q in  $62$ ,  $62_a$  and  $62_b$  was identified from modulated off-resonance experiments.


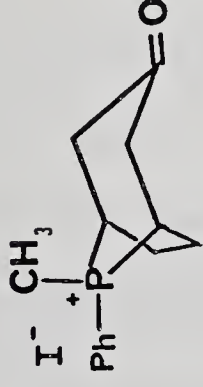

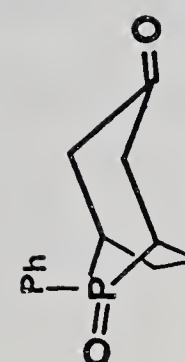
The configuration,  $62$ , of the major isomer of 8-phospha-bicyclo[3.2.1]octan-3-one has been proved by earlier pmr studies<sup>126</sup>. The equatorial phenyl C-q carbon in  $62$  exhibits an identical chemical shift to that in  $58\beta$  (131.8 ppm), indicating that no significant  $\gamma$ -effect is induced by the ethylene bridge. This is somewhat surprising since in the analogous N-methyl tropanone ( $34$ ) the N-methyl carbon is shielded (-6.8 ppm) compared to N-methyl-4-piperidone<sup>43</sup>. This anomaly suggests that the phenyl orientation may be incorrectly assigned or that the model is bad. This feature can be investigated further by analyzing the  $^2J_{PC}$  couplings. Thus the larger  $^2J_{PC}$  coupling constant at C-2,4 (14.6 Hz) compared to C-6,7 (4.9 Hz) confirms the cis-relationship between the phosphorus lone-pair and the carbons C-2,4. The phenyl group, therefore, must be equatorially oriented and consequently no significant  $\gamma$ -effect is induced by the ethylene bridge in these compounds.

Changes in the phosphorus atom hybridization are reflected in the  $^1J_{PC}$  coupling constants in the phosphonium salt  $63$ , compared to  $62$ .  $^1J_{PC}$ , is enhanced by 39 Hz at C-1,5 and by 63 Hz at C-q. The  $\beta$ -effects of the methyl group are shielding at C-q (-11.5 ppm) and at C-1,5 (-4.9 ppm), while in the analogous N-methyl derivative the effects are -7.5 ppm and +4.9 ppm, respectively (Chapter III, Table XII,  $34$ ,



TABLE XXII

$^{13}\text{C}$  Chemical Shifts and  $J_{\text{P-C}}$  Coupling<sup>a</sup> Constant of 8-phosphabicyclo[3.2.1]octan-3-one Derivatives

Carbon Position	Structure			
				
	$\text{CDCl}_3$	$\text{DMSO-d}_6^b$	$\text{D}_2\text{O}^c$	$\text{CDCl}_3$
C-1,5	36.3 <sub>9</sub> (11.0)	31.4 <sub>6</sub> (48.8)	29.9 <sub>5</sub> (50.0)	30.1 <sub>0</sub> (65.9)
C-2,4	49.2 <sub>0</sub> (14.6)	46.0 <sub>3</sub> (broad)	44.6 <sub>8</sub> (4.9)	44.9 <sub>1</sub> (6.1)
C-3	210.6 <sub>7</sub> (0)	205.8 <sub>6</sub> (3.7)	208.9 <sub>1</sub> (6.1)	208.0 <sub>0</sub> (7)
C-6,7	29.6 <sub>7</sub> (4.9)	26.8 <sub>5</sub> (8.6)	25.5 <sub>5</sub> (8.6)	23.2 <sub>8</sub> (13.4)
P-CH <sub>3</sub>		6.2 <sub>1</sub> (44.0)	4.8 <sub>7</sub> (45.2)	
C-q	131.9 <sub>3</sub> (18.3)	120.2 <sub>8</sub> (81.8)	116.4 <sub>3</sub> (81.8)	130.7 <sub>2</sub> (42.7)
C-o	d	133.6 <sub>1</sub> (8.5)	131.6 <sub>3</sub> (9.7)	d
C-m	d	131.4 <sub>2</sub> (12.2)	130.5 <sub>0</sub> (12.2)	d
C-p	d	136.0 <sub>6</sub> (0)	135.6 <sub>6</sub> (0)	d

<sup>a</sup> Given in Hertz shown in parentheses, sign not determined. <sup>c</sup> Converted to TMS scale using:  $\delta_{\text{C}}^{\text{Dioxane}} = 66.74$  ppm.

<sup>b</sup> Converted to TMS scale using:  $\delta_{\text{C}}^{\text{DMSO-d}_6} = 41.17$  ppm. <sup>d</sup> Not obtainable due to overlapping of resonances.



34b). At the present time no explanation for the shielding effect at C-1,5 in  $\underline{63}$  can be given.

Isolation of the oxide isomers  $\underline{62a}$  and  $\underline{62b}$  was not possible. Therefore, the chemical shifts were obtained from mixtures by comparing the relative intensities of the resonances, and by the use of additivity effects. As already mentioned an axial oxygen has a larger  $\gamma$ -effect than an equatorial one. Hence, C-2,4 in  $\underline{62a}$  is expected to be at high field compared to  $\underline{62b}$ , i.e., 44.9<sub>1</sub> ppm in  $\underline{62a}$ , 47.4<sub>2</sub> ppm in  $\underline{62b}$ . A shielding  $\beta$ -effect (-6.3 ppm) at C-1,5 of an axial oxygen in  $\underline{62a}$  compared to  $\underline{62}$  is observed and differs from the deshielding (+3.0 ppm) found in  $\underline{55a}$  compared to  $\underline{55}$  (Table XVII) where the oxygen is also axial.

The cmr results confirm the conformation of  $\underline{62}$  to be a chair with the phenyl group equatorial, in agreement with the pmr data<sup>121</sup>. In the bicyclic system ( $\underline{62}$ ) introduction of a substituent at the phosphorus atom causes a shielding effect at C-1,5 in  $\underline{63}$  and  $\underline{62a}$  as opposed to the deshielding  $\beta$ -effect in the tropanes (Chapter III) and 1-oxo-1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanol  $\underline{55a}$ .

## 5. Phosphorus, Nitrogen and Carbon Comparisons

As indicated in the above discussion, many phosphorus heterocyclic compounds are characterized by the preference for the substituent on the phosphorus atom to take up the axial configuration unless other driving forces - steric strain, hydrogen bonding, etc., enhance a change in conformation. This feature contrasts the phosphorus systems from analogous carbon and nitrogen compounds in which substituents prefer the equatorial configuration. However, application of the parameters



obtained earlier, for changing the phenyl group from an axial to equatorial orientation, to  $\delta_{\sim}$  51 and  $\delta_{\sim}$  15 enables estimation of the carbon chemical shifts for molecules with an equatorial phenyl group. The resulting chemical shifts are shown in Figure 12.

It is valuable to consider Pauling's electronegativity values for P(2.1), C(2.5) and N(3.0) in relation to the observed chemical shifts. Introduction of an electropositive phosphorus atom in place of carbon appreciably changes the local charge density on the adjacent carbon atoms. The consequent shielding is apparent from the upfield shift (-7.7 ppm) at C-2,6 in  $\delta_{\sim}$  51 (equat. Ph) compared to phenyl cyclohexanone. The effect is attenuated at C-3,5 (-2.2 ppm) and C-4 (+0.9 ppm). The analogous effects between the phosphorus and nitrogen heteroatoms are C-2,6 (-23.8 ppm), C-3,5 (-1.0 ppm) and C-4 (+2.5 ppm). Applying the additivity parameters for changing the nitrogen substituent from methyl to phenyl in the corresponding piperidines ( $\beta$  -6.0,  $\gamma$  -0.2,  $\delta$  +0.5 ppm - Figure  $\delta_{\sim}$  12 and Table VII) to N-methyl-4-piperidone and 1,3,5-trimethyl-4-piperidone enables a comparison to be made with the analogous phosphorus compounds. (Chemical shifts of the N-phenylpiperidines are given in Figure  $\delta_{\sim}$  12.) The overall effects are similar to those in the unsubstituted compound: C-2,6 (-23.2), C-3,5 (-1.2) and C-4 (+2.6 ppm) in the monomethyl and C-2,6 (-22.2), C-3,5 (-0.3) and C-4 (+2.1 ppm) in the trimethyl compounds.

The  $\gamma$ -effect of  $\text{CH}_2$ , N and P can be compared by considering the equatorial methyl shifts in 2,5-dimethylcyclohexane,  $\delta_{\sim}$  17 and  $\delta_{\sim}$  58 $\beta$ .



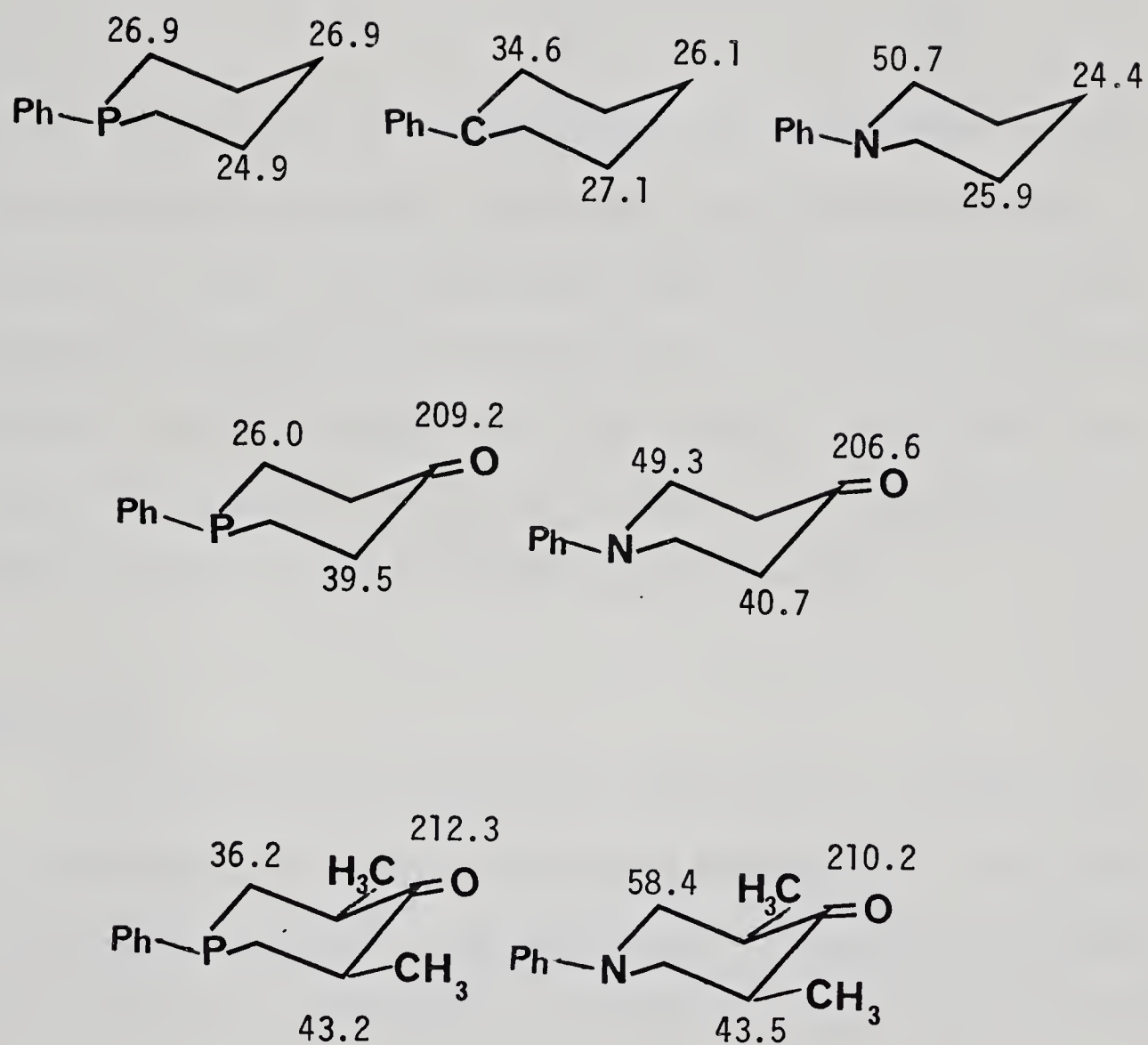
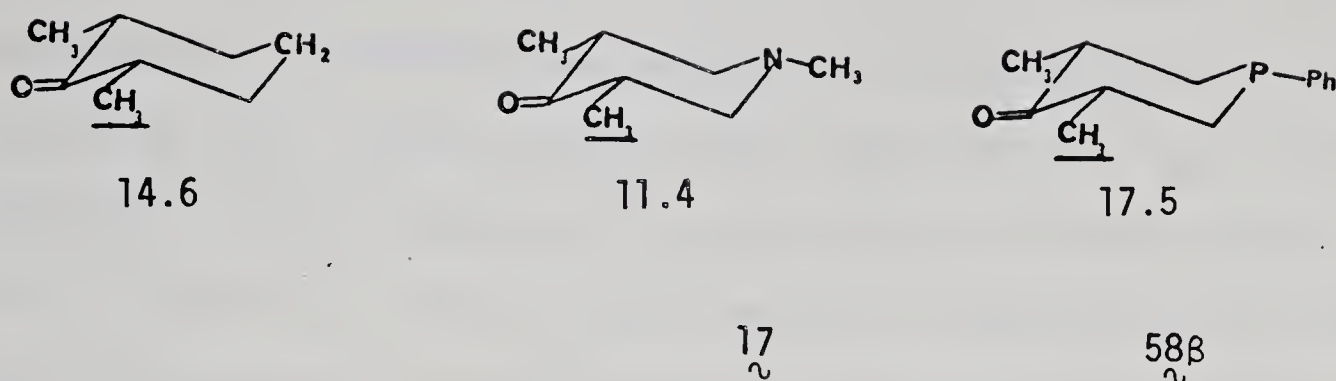


FIGURE 12: Carbon-13 chemical shifts for C-2,6, C-3,5 and C-4 carbon positions in analogous C, N and P six-membered rings.





Compared to cyclohexanone the nitrogen atom shields the methyl carbon while the phosphorus deshields. The former observation has already been described (Chapter II(A)) while the latter follows from the fact that third-row heteroatoms are expected to have  $\gamma$ -deshielding effects<sup>34</sup>. The phosphorus  $\gamma$ -effect appears to be quite general. From this study it is clear that phosphorus should be included as a  $\gamma$ -deshielding heteroatom for nuclei in the anti-periplanar arrangement.

#### D. CONCLUSIONS

This study clearly demonstrates that cmr is a valuable tool in the conformational analysis of phosphorus heterocycles. In particular,  $^2J_{PC}$  coupling constants in phosphorinane derivatives are extremely useful in confirming conformational assignments. The phenyl orientation is assigned as equatorial in 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanol (55) rather than axial due to the observed coupling (11 Hz) to the C-3,5 carbons. It is imperative that the dihedral angle and sign of the phosphorus-carbon coupling constants in phosphorus heterocycles should be obtained so that a definite geometric relationship of the  $^2J_{PC}$  coupling constant can be calculated. From our work we submit the approximation that the maximum coupling of 33 Hz occurs with the dihedral angle of  $0^\circ$  with a steady decrease in coupling to 11 Hz at



60° and 0 Hz at 180°. Distant dependent coupling was observed in the phosphorinane and phosphorinane oxides with the exception that in the latter the  $^3J_{PC}$  coupling constants were larger than the  $^2J_{PC}$  coupling constants. A steric-effect on  $^1J_{PC}$  was observed with the coupling being larger to C-q when the phenyl groups was equatorial in the phosphorinanes and when the phenyl group was axial in the phosphorinane oxides.

The chair conformation of the phosphorinanes was preferred with the phenyl substituent predominately axial, with the exception of 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanol ( $\hat{55}$ ) in which two severe 1,3-diaxial interactions cause the chair to interconvert to the conformer with an equatorial phenyl group. The conformational changes in the molecules investigated were better followed by the  $^2J_{PC}$  coupling constant than  $^{13}C$  chemical shifts. The conformation of the phosphorinane oxides were found similar to the phosphorinanes, in contrast with the sulphide derivative of 1-phenylphosphorinane which are reported<sup>73a</sup> to undergo chair interconversion upon sulphurization. Additivity effects of sulphur and oxygen in the corresponding derivatives of 1-phenyl-2,2,6,6-tetramethyl-4-phosphorinanone ( $\hat{54}$ ) are similar with the exception that the  $\beta$ -effect of sulphur on C-2,6 is larger than that of oxygen.

The fact that no significant electron delocalization occurs from the phosphorus to the aromatic rings in arylphosphines was confirmed by the cmr study on mono-, di- and triphenylphosphine, while the electron withdrawing effect of the phosphorus-oxygen bond in the phosphine oxides of these molecules was clearly observed with the phosphorus-oxygen bond being significantly polarized ( $P^{\oplus} - O^{\ominus}$ ).



## E. EXPERIMENTAL

A sample of triphenylphosphine was obtained from Aldrich Chemical Company and used without further purification. A sample of 1-methoxy-1-oxo-4-phosphorinanone was donated by Dr. M. J. Gallagher. The compounds that were prepared by well-known methods along with the observed physical constants are given below. In all cases the boiling points and melting points are uncorrected.

<u>Compound</u>	<u>Observed</u> bp/mm or mp	<u>Reported</u> bp/mm or mp	<u>Ref.</u>
2,2,6,6-tetramethyl-1-phenyl-4-phosphorinanone	90°	91-92°	127
2,2,6,6-tetramethyl-1-phenyl-1-oxo-4-phosphorinanone	209-210°	212-213°	127
2,2,6,6-tetramethyl-4-phenyl-1-sulfide-4-phosphorinanone	135-138°	138°	127
2,2,6,6-tetramethyl-1-phenyl-4-phosphorinanol	122-124°	123-124°	127
1-phenyl-4-phosphorinanone	184-190°/1mm	185-190°/1mm	128
1-phenyl-1-oxo-4-phosphorinanone	164-166°	166°	129
1-phenylphosphorinane	192-194°/3mm	140°/1mm	130
1-phenyl-1-oxophosphorinane	126-128°	130°	131
8-phenyl-9-phosphabicyclo[3.2.1.]octan-3-one	143-145°	144-146°	126
8-phenyl-8-methyl-8-phosphonium-bicyclo[3.2.1.]octan-3-one iodide	238-240°	239-240°	126
phenylphosphine	154-157°/730mm	155°/760mm	132
phenylphosphine oxide	81-82°	80-83°	133
diphenylphosphine	122-125°/1mm	150-154°/11mm	134
diphenylphosphine oxide	53-55°	53-55°	135
triphenylphosphine oxide	153-155°	154-155°	136



<u>Compound</u>	<u>Observed</u> bp/mm or mp	<u>Reported</u> bp/mm or mp	<u>Ref.</u>
N-phenylpiperidine	115°/10mm	110-118°/9mm	137

### Synthesis of Phosphorinane and Arylphosphine Oxides

Following a reported procedure<sup>126</sup> the phosphorinane or arylphosphine was dissolved in acetone (pH  $\approx$  8) and an excess of 30% H<sub>2</sub>O<sub>2</sub> was added, dropwise to the cooled solution. The mixture was stirred for 2 hrs., diluted with more acetone and washed several times with 5% FeSO<sub>4</sub> solution, then with water and then dried (MgSO<sub>4</sub>). Evaporation left the oxide product which can be purified by recrystallization from ether.

### 2,2,6,6-Tetramethyl-1-phenylphosphorinane

A mixture of 3.85 g of the tetramethyl-4-phosphorinanone<sup>127</sup>, 3 g of sodium hydroxide, 3.5 g of 85% aqueous hydrazine and 50 mls of diethylene glycol was refluxed at 195° for 3 hrs. It was allowed to cool, neutralized with concentrated hydrochloric acid, extracted with benzene and freeze dried. A yield of 1 g (55%) of the title compound was obtained. B.p. 60-63°.

Pmr (CDCl<sub>3</sub>) CH<sub>3</sub>(ax.) 1.2<sub>8</sub> ppm J<sub>PH</sub>:19 Hz, CH<sub>3</sub>(eq) 0.8<sub>1</sub> ppm, J<sub>PH</sub> 10 Hz,

CH<sub>2</sub>'s 1.7 ppm (multiplet). Phenyl 7.6 - 7.9 ppm multiplet.

Characterized by formation of the oxide derivative.

### 2,2,6,6-Tetramethyl-1-phenyl-1-oxo-phosphorinane

Procedure as given above yielded a hygroscopic white solid of mp 60°.

Pmr (CDCl<sub>3</sub>) CH<sub>3</sub>(ax.) 1.30 ppm J<sub>PH</sub>:12.5 Hz, CH<sub>3</sub>(eq) 1.0<sub>1</sub> ppm J<sub>PH</sub> 14 Hz,

CH<sub>2</sub>'s 1.5-2.0 ppm (multiplet) phenyl, o 7.7-8.0 ppm (multiplet), m and



p 7.4-7.6 ppm (multiplet).

I.R. (Nujol) P=O (st):1130  $\text{cm}^{-1}$ , P-Ph (st):1460  $\text{cm}^{-1}$ .

Mass Spec. Exact Mass. 250.1478 (measured) 250.1483 (calculated.)

Correct for  $\text{C}_{15}\text{H}_{23}\text{OP}$ .

### 2,2,6,6-Tetramethyl-1-phenyl-1-oxo-4-Phosphorinanol

Procedure as given above yielded a white solid, mp 197-200 .

Pmr ( $\text{CDCl}_3$ )  $\text{CH}_3(\text{ax.})$  1.50 ppm,  $J_{\text{PH}}$  12 Hz,  $\text{CH}_3(\text{eq})$  1.12 ppm,  $J_{\text{PH}}$  12 Hz, CH and  $\text{CH}_2$  1.7-2.4 ppm (multiplet). Phenyl o, 7.7-8.0 ppm (multiplet), m and p 7.4 - 7.6 ppm (multiplet).

I.R. Nujol) 3320  $\text{cm}^{-1}$  (OH str), 1440  $\text{cm}^{-1}$  (P-Ph str), 1140  $\text{cm}^{-1}$  P=O (str).

Mass.Spec. Exact Mass. 266.1432 (measured), 266.1436 (calculated).

Correct for  $\text{C}_{15}\text{H}_{23}\text{O}_2\text{P}$ .

### 1-Phenyl-3,5-Dimethyl-4-Phosphorinanone

A mixture of 5 g of 2,4-dimethyl-3-pentadienone<sup>89</sup> and 5 g of phenylphosphine was heated under a nitrogen atmosphere at 60° for 3 hrs. The product was a heavy oil that could only be distilled at high temperature, bp 140°/0.2mm, lit. 103°/0.01mm. The product was subjected to column chromatography on alumina eluting with chloroform, the column being kept under a nitrogen atmosphere. The first fraction collected was a mixture of 3 isomers (cmr data given in Table XX). Further chromatography of this fraction using benzene as elutant separated one of the isomers since the major fraction collected was only a mixture of two isomers (two spots on t.l.c.). Further chromatography did not resolve these isomers.

Pmr ( $\text{CDCl}_3$ ) of the three isomers:



CH<sub>3</sub> 0.9<sub>8</sub> ppm, J<sub>CH</sub> 6.4 Hz ( $\underset{\sim}{58\beta}$ ), CH<sub>3</sub> 1.0<sub>8</sub> ppm J<sub>CH</sub> 6.5 Hz ( $\underset{\sim}{58\alpha}$ ), CH<sub>3</sub> 1.2<sub>4</sub> ppm(s)  $\underset{\sim}{58\gamma}$  (other methyl resonances observed). CH<sub>2</sub>'s 1.7 - 2.1 ppm (multiplet) CH's 2.2 - 2.6 ppm (multiplet) Phenyl 7.1 - 7.4 ppm (multiplet).

1-Phenyl-1-oxo-3,5-dimethyl-4-phosphorinone

A mixture of the isomers,  $\underset{\sim}{58\alpha}$  and  $\underset{\sim}{58\beta}$ , with the former isomer dominating was subjected to oxidation as outlined earlier. A white solid of mp 122-125° was isolated which was shown by t.l.c. to be a single component. Mp (lit<sup>120</sup>) 124-126°.

I.R. (Nujol) 1720 cm<sup>-1</sup> (C=O str), 1160 cm<sup>-1</sup> P=O (str) and 1440 cm<sup>-1</sup> P-PH (str).

Mass spec. m/e 236.

8-Phenyl-8-oxo-8-phosphabicyclo[3.2.1.]octan-3-one.

A 1.1g mixture of the two isomers of 8-Phenyl-8-phosphabicyclo[3.2.1.]octan-3-one was subjected to oxidation as outlined earlier using 0.61 g of 30% H<sub>2</sub>O<sub>2</sub>. The resulting crystalline solid after recrystallization from acetonitrile yielded 1 g of the title compound, m.p. 200-203°, however, two isomers were present as indicated by t.l.c. These isomers could not be separated using column chromatography.

I.R. (Nujol) 1750 cm<sup>-1</sup> (C=O str), 1450 cm<sup>-1</sup>, P-Ph (str) 1125 cm<sup>-1</sup> P=O (str).

Mass spectrum m/e 234.



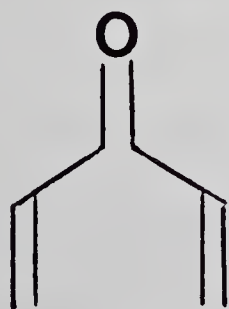
## CHAPTER V

### DIENONES

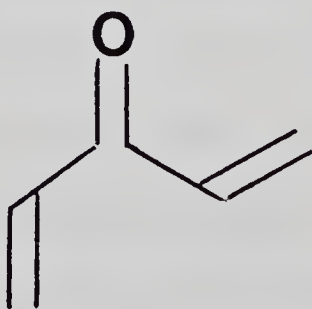
#### A. INTRODUCTION

Dienones are a particular example of cross-conjugated systems. We define cross-conjugation, following Phelan and Orchin<sup>138</sup>, as a compound possessing three unsaturated groups, two of which although conjugated to a third unsaturated center are not conjugated to each other. The review article by Phelan and Orchin primarily concerns a molecular orbital approach to the electronic distribution and extent of conjugation between the nonconjugated centers in cross-conjugated systems, however, little reference is made to dienones. There is also a paucity of spectroscopic information on dienones. In particular only a few cholest-1,4-dien-3-one derivatives<sup>139</sup>, phorone<sup>83</sup> and piperitenone<sup>83</sup> have been studied using carbon-13 nmr methods. Carbon-13 is ideally suited to a study of such molecules since both the extent of electron distribution and conjugation can be studied using this technique.

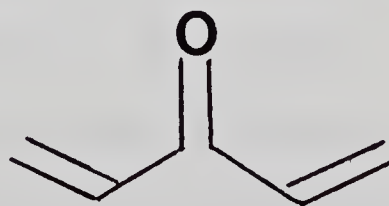
In the acyclic dienone system there are three possible planar conformations. However alkyl substitution at any of the olefinic



a: s-trans/s-trans  
~



b: s-trans/s-cis  
~



c: s-cis/s-cis  
~



carbons is expected to have a dramatic effect on the dienone conformation so presenting the dienone system with two opposing forces: conjugative and steric. In all cyclic dienone systems the propensity for the dominance of conjugative forces is greater due to the imposed planarity of the ring.

Synthetic interest in dienones has been generated due to their ability to undergo condensation with primary amines (Chapter II) and primary phosphines (Chapter IV) to form nitrogen and phosphorus heterocyclic compounds, respectively. This method has been used greatly in the present work. A synthetic route to cyclopentenones via an acid-catalyzed cyclization of dienones has also recently been reported<sup>140</sup>. A better knowledge of the electronic distribution and extent of conjugation present in dienones is considered necessary.

A basic unit of any dienone is the  $\alpha,\beta$ -unsaturated carbonyl system. The  $^{13}\text{C}$  chemical shifts of the olefinic and carbonyl carbon nuclei of various  $\alpha,\beta$ -unsaturated carbonyl compounds have been reported<sup>83</sup>. The variation of the olefinic shielding with alkyl substitution parallels that observed in olefinic hydrocarbons<sup>141</sup>. However, only two dienones, phorone and piperitenone have been examined using cmr and the olefinic and carbonyl carbon chemical shifts reported<sup>83</sup>. It was suggested by Marr and Stothers<sup>83</sup> that the high field shift of the carbonyl carbon in these dienones, compared to other  $\alpha,\beta$ -unsaturated compounds was due to the additional electron density at the carbonyl carbon induced by the second double bond. In view of this statement and the conformational problem the dienones present we have determined the carbon-13 chemical shifts of a series of dienones, both acyclic and alicyclic, in order to define some general features of the dienone



cross-conjugated system.

## B. RESULTS

The carbon-13 chemical shifts for the acyclic dienones and enones studied are given in Table XXIII. Results for the alicyclic rigid dienones and supporting structures are given in Table XXIV. Assignments were made using conventional techniques. Ambiguities in assignment remain for the methyl resonances in compounds  $\underline{65}$ ,  $\underline{69}$  and  $\underline{70}$ . In compound  $\underline{69}$ , C-2 is distinguished from C-4 by the typical  $\beta$ -deshielding effect<sup>83</sup> induced by the C-1' methyls at the C-2 position. The carbon-13 shifts in  $\underline{66}$ ,  $\underline{72}$  and  $\underline{78}$  were taken from the literature<sup>83,97,105b</sup>. Distinction between C-1 and C-5 in  $\underline{67}$  was made by comparing the former chemical shift with that of the analogous position in the enone,  $\underline{66}$ . The chemical shifts of  $\underline{76}$  were re-determined and compared favourably with the literature values<sup>142</sup>. The methylene carbons in  $\underline{73}$ ,  $\underline{77}$  and  $\underline{79}$  were identified by use of the endocyclic homoallylic-effect<sup>143</sup>. Distinction between the  $\alpha$  and  $\beta$ -olefinic carbons in  $\underline{81}$  was made using a proton-selective decoupling experiment.

## C. DISCUSSION

### 1. Olefinic and Carbonyl Carbons

From the carbon chemical shifts of the  $\alpha$ - and  $\beta$ -olefinic carbons in both the symmetrical acyclic,  $\underline{68}$ ,  $\underline{70}$  and  $\underline{71}$ , and rigid alicyclic  $\underline{74}$  and  $\underline{81}$  dienones, it can be stated that there exists a contribution from the resonance forms  $\underline{d}$  and  $\underline{f}$  to the dienone structure. That is, the  $\beta$ -olefinic carbon is to low field in all cases. In



TABLE XXIII

Carbon-13 Chemical Shifts<sup>a</sup> of Some Acyclic Enones and Dienones

Carbon Position	64 $\delta_c$	65 $\delta_c$	66 $\delta_c$	67 $\delta_c$	68 $\delta_c$	69 $\delta_c$	70 $\delta_c$	71 $\delta_c$
C-1	26.2 <sub>7</sub>	27.4 <sub>6</sub>	b	125.1 <sub>6</sub>	124.5 <sub>7</sub>	(20.8 <sub>8</sub> )	(20.4 <sub>4</sub> )	143.1 <sub>2</sub>
C-2	198.0 <sub>9</sub>	197.9 <sub>3</sub>	198.8	145.0 <sub>1</sub>	144.5 <sub>8</sub>	156.5 <sub>0</sub>	153.8 <sub>6</sub>	125.4 <sub>8</sub>
C-3	137.7 <sub>1</sub>	124.3 <sub>5</sub>	144.3	192.2 <sub>1</sub>	199.3 <sub>9</sub>	122.3 <sub>0</sub>	126.2 <sub>9</sub>	188.6 <sub>5</sub>
C-4	128.5 <sub>0</sub>	154.5 <sub>0</sub>	125.1	131.7 <sub>9</sub>	144.5 <sub>8</sub>	189.8 <sub>4</sub>	191.1 <sub>3</sub>	125.4 <sub>8</sub>
C-5		(20.5 <sub>0</sub> ) <sup>c</sup>		128.5 <sub>0</sub>	124.5 <sub>7</sub>	138.5 <sub>5</sub>	126.2 <sub>9</sub>	143.1 <sub>2</sub>
C-6						126.6 <sub>6</sub>	153.8 <sub>6</sub>	
C-7							(20.4 <sub>4</sub> )	
C-2'		(31.5 <sub>0</sub> )		17.7 <sub>5</sub>	18.5 <sub>0</sub>	(27.3 <sub>7</sub> )	(27.6 <sub>2</sub> )	
C-3'			b					
C-4'					18.5 <sub>0</sub>			
C-6'							(27.6 <sub>2</sub> )	

<sup>a</sup> Solvent CDCl<sub>3</sub> except 66  $\delta_c$ . Original data converted using  $\delta_c^{CS_2} = 192.8$ .<sup>b</sup> Reference 83, methyl resonances not reported. Solvent effect accounted for by comparison of shifts 64, 65 and 66. Neat versus CDCl<sub>3</sub>.<sup>c</sup> Parenthesis indicate some uncertainty in assignment.



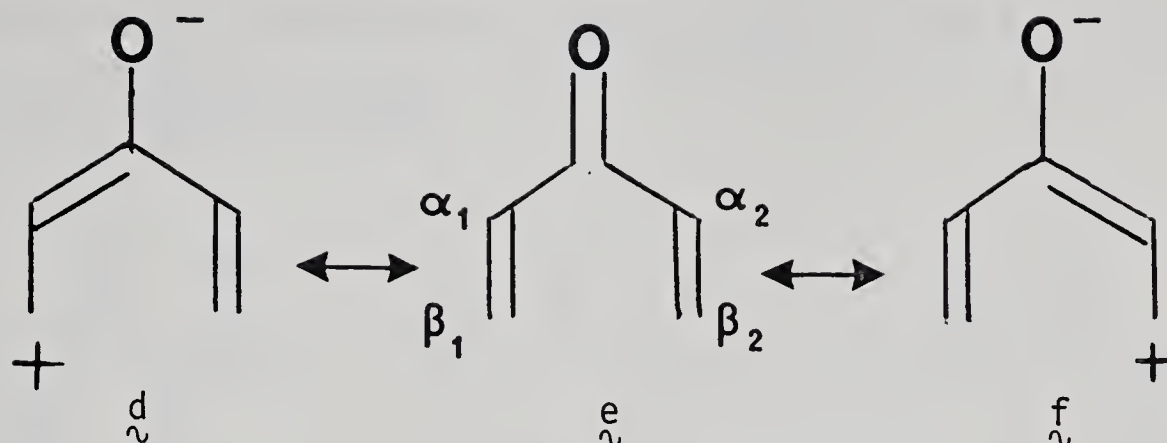
TABLE XXIV

Carbon-13 Chemical Shifts<sup>a</sup> of Alicyclic Enones, Dienones and Supporting Derivatives

Structure		72 <sup>b,c</sup>	73	74	75	76	77	78 <sup>b</sup>	79	80	81
Carbon Position											
C-1		209.4	198.4 <sub>1</sub>	185.0 <sub>9</sub>	187.1 <sub>9</sub>	203.7 <sub>0</sub>	191.1 <sub>3</sub>	210.5	198.6 <sub>8</sub>	214.6 <sub>5</sub>	192.4 <sub>3</sub>
C-2		38.0	126.8 <sub>3</sub>	127.2 <sub>1</sub>	136.5 <sub>9</sub>	131.8 <sub>4</sub>	128.9 <sub>3</sub>	49.0	125.3 <sub>7</sub>	43.8 <sub>0</sub>	133.5 <sub>2</sub>
C-3		39.5	159.2 <sub>5</sub>	156.5 <sub>5</sub>	136.5 <sub>9</sub>	28.5 <sub>9</sub>	28.0 <sub>0</sub>	29.5	159.6 <sub>3</sub>	(30.4 <sub>2</sub> ) <sup>d</sup>	144.0 <sub>4</sub>
C-4		30.2	32.7 <sub>4</sub>	37.8 <sub>2</sub>	187.1 <sub>9</sub>	32.8 <sub>5</sub>	31.8 <sub>3</sub>	47.2	50.7 <sub>6</sub>	(24.3 <sub>3</sub> )	27.3 <sub>0</sub>
C-5		39.5	36.2 <sub>0</sub>	156.5 <sub>5</sub>	136.5 <sub>9</sub>	31.5 <sub>6</sub>	159.4 <sub>1</sub>	35.1	33.3 <sub>9</sub>	(24.3 <sub>3</sub> )	27.3 <sub>0</sub>
C-6		38.0	34.3 <sub>6</sub>	127.2 <sub>1</sub>	136.5 <sub>9</sub>	50.8 <sub>1</sub>	128.9 <sub>3</sub>	53.9	45.0 <sub>4</sub>	(30.4 <sub>2</sub> )	144.0 <sub>4</sub>
C-2'						141.7 <sub>7</sub>	142.1 <sub>0</sub>				
C-2"						{22.98}	{22.50}				
						(22.1 <sub>1</sub> )	(22.8 <sub>2</sub> )				
C-3'								22.4	24.3 <sub>2</sub>		
C-4'		27.8	27.6 <sub>7</sub>	26.6 <sub>0</sub>				25.7			
C-5'						21.7 <sub>4</sub>	23.7 <sub>4</sub>	32.0	28.2 <sub>1</sub>		
C-7										43.8 <sub>0</sub>	133.5 <sub>2</sub>

<sup>a</sup> Given in ppm downfield from TMS. Solvent CDCl<sub>3</sub> except 72 CS<sub>2</sub>, original data converted using  $\delta_{\text{C}}^{\text{CS}_2} = 192.8$  ppm.<sup>b</sup> Taken from the literature: 72 reference 105b, 78 reference 97.<sup>c</sup> Numbering system is shown in 72, increasing in an anti-clockwise direction.<sup>d</sup> Parenthesis indicate some uncertainty in assignment.



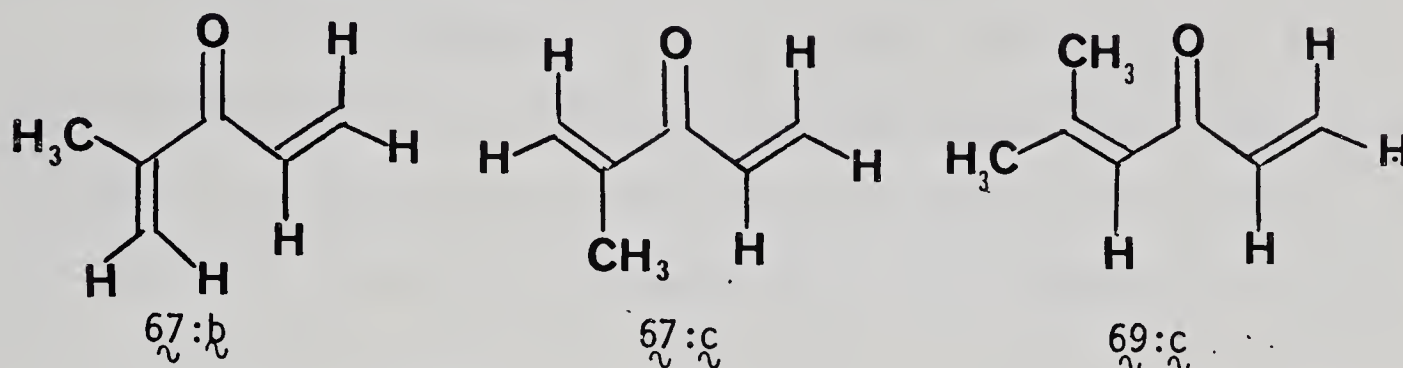


general the carbonyl group is shielded on introduction of a second double bond to the enone. A greater conjugative effect is experienced by the carbonyl group in the dienone and where the conjugative ability is further extended, as in the phenyl compound  $\tilde{71}$ , the shielding is greatest (188.6<sub>5</sub> ppm) in the acyclic systems.

The conformation of the dienone is important when considering the additivity effects of the second double bond. In the acyclic systems, comparison of  $\tilde{66}$  and  $\tilde{67}$  give the double bond substitution parameters at the carbonyl,  $\alpha$ - and  $\beta$ -olefinic carbons, -6.6, +0.7 and 0.0 ppm, respectively. While a similar comparison between  $\tilde{65}$  and  $\tilde{69}$  gives the values, -8.1, -2.0 and +2.0 ppm, respectively. Since any effects on the carbonyl and  $\beta$ -olefinic carbons are due to conjugative interactions the larger shielding (-8.1 ppm) at the carbonyl carbon and deshielding (+2.0 ppm) at the  $\beta$ -olefinic carbon in  $\tilde{69}$  than  $\tilde{67}$  (-6.6 and 0.0 ppm, respectively) is indicative of a greater extent of conjugation in the former. Mesityl oxide  $\tilde{65}$  is known to exist in the *s-cis* conformation<sup>83</sup>. Thus the dienone is conversely assumed to exist in the linear  $\tilde{c}$  formation. The  $\tilde{c}$  and  $\tilde{b}$  conformations of  $\tilde{67}$  have interactions between the methyl or C-1 olefinic proton with the C-4 olefinic proton, respectively. These interactions will likely cause a rotation of one of the double bonds out of the



conjugative plane, hence lowering the conjugative effect at the carbonyl and  $\beta$ -olefinic carbons.



The cyclic dienones impart rigidity in the molecule and this appears to assist conjugation. Introduction of the double bond in  $\underline{72}$  causes a carbonyl shielding of -11.0 ppm, similar to the effect observed in 2-cyclohexenone (-11.7 ppm)<sup>83</sup> and isophorone  $\underline{79}$  (-11.8 ppm). The dienone  $\underline{74}$  exhibits a carbonyl chemical shift of 185.0<sub>g</sub> ppm, at higher field than even p-benzoquinone  $\underline{75}$  (187.1<sub>g</sub> ppm). This suggests that  $\underline{74}$  is relatively planar. The shielding effect of -13.3 ppm is the largest observed in the dienone series. An x-ray study<sup>144</sup> of the similar compound, spirodienone, where the C-4' methyls of  $\underline{74}$  are part of a cyclohexanone ring provides evidence for a planar conformation. Introduction of the second double bond causes the  $\alpha$ - and  $\beta$ -olefinic carbons of the enone to be deshielded (+0.4 ppm) and shielded (-2.7 ppm), respectively. The latter effect is dominated by an endocyclic homoallyl shielding effect. Comparing the shifts in pulegone  $\underline{76}$  and pipertenone  $\underline{77}$  indicates that the carbonyl group is shielded (-12.6 ppm) while the  $\alpha$ - and  $\beta$ -olefinic carbons are deshielded (+2.9 ppm) and shielded (-0.3 ppm), respectively. Again the large carbonyl shielding is indicative of a large increase in conjugation in  $\underline{77}$  as a consequence of its planar configuration. Pulegone is considered to be



a chair structure undergoing chair-chair interconversion. From Dreiding models, pipertenone appears to be almost planar with C-3 projecting slightly out of the plane of the ring.

Cycloheptadienone  $\underset{\sim}{81}$  is an extremely rigid molecule, the double bonds causing the carbonyl of cycloheptanone (214.6<sub>5</sub> ppm) to be shielded (-22.2 ppm) which compares to the similar shift difference in  $\underset{\sim}{72}$  (-23.7 ppm) indicating the dienone part of the ring in  $\underset{\sim}{81}$  is planar.

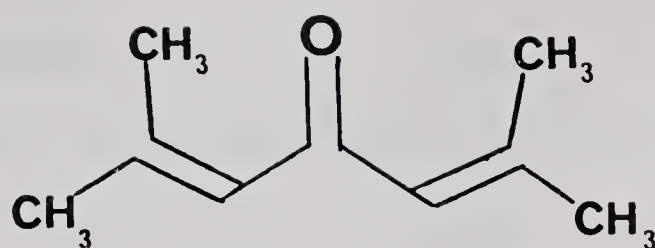
## 2. Methyl Carbons

The methyl groups in  $\underset{\sim}{65}$ ,  $\underset{\sim}{69}$  and  $\underset{\sim}{70}$  can be assigned with the methyl cis to the carbonyl group being to low field. Comparison of  $\underset{\sim}{65}$  and  $\underset{\sim}{69}$  shows that one of the methyl resonances is deshielded by 4.1 ppm. It is expected that the anisotropic effect of the carbonyl group may be different in the dienone so causing greater deshielding of the cis methyl since the conformations of both  $\underset{\sim}{65}$  and  $\underset{\sim}{69}$  are s-cis.

The effect of methyl substitution at the  $\alpha$ -olefinic carbon on the dienone  $\underset{\sim}{67}$  results in deshielding of the carbonyl carbon (+7.2 ppm) while similar substitution in the enone  $\underset{\sim}{64}$  causes only a 0.7 ppm deshielding effect. This difference is due to a conformational change in  $\underset{\sim}{67}$  to  $\underset{\sim}{68}$ . The dienone  $\underset{\sim}{68}$  is considered to be a non-planar molecule since severe 1,5-steric interactions occur in the planar conformation. Thus the carbonyl deshielding in  $\underset{\sim}{68}$  is taken to represent a decrease in conjugation rather than an  $\alpha$ -methyl substituent effect.

The conformation of  $\underset{\sim}{70}$  is expected to be similar to the planar  $\underset{\sim}{c}$  conformation of  $\underset{\sim}{69}$  since the methyl resonances are identical in both dienones. Hence the two  $\beta$ -methyl substituent effects can be obtained, carbonyl (-1.3 ppm),  $\alpha$ -olefin (-12.4 ppm)  $\beta$ -olefin (+27.3 ppm).

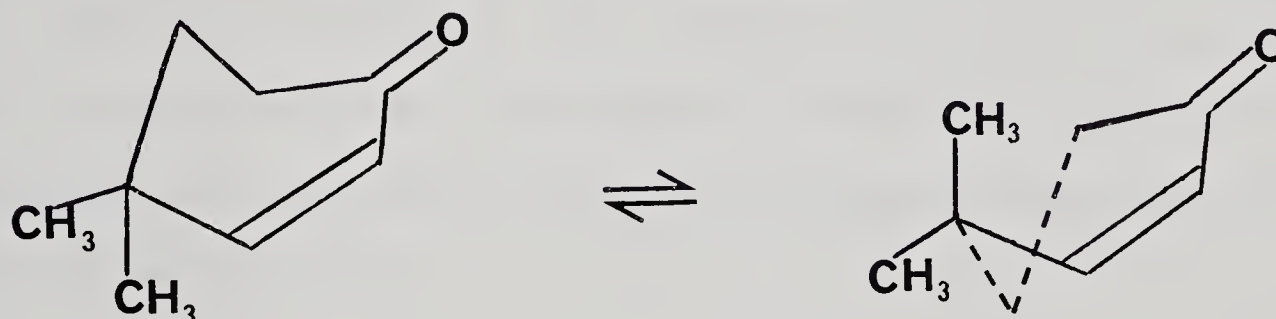




70:c  
~ ~

These values compare favourably with those between the enones  $\tilde{64}$  and  $\tilde{65}$ , -0.2, -13.4 and +26.0 ppm, respectively. The 1 ppm difference in these parameters may arise from conformational differences since the conformation of  $\tilde{64}$  is not known.

On examining Drieding models the equivalence of the C-4' methyls in  $\tilde{73}$  suggest the molecule exists in a half-chair conformation in equilibrium:



The C-5' methyls are also equivalent (28.2<sub>1</sub> ppm) in  $\tilde{79}$  supporting the half-chair conformational equilibrium in this molecule.

#### D. CONCLUSIONS

The substitution effect of the second double bond on the carbonyl carbon in the acyclic dienone series has a lower shielding effect (-8.1 ppm) than found upon formation of the enone (-9.4 ppm, calculated from acetone 207.5 ppm<sup>85</sup>, methyl vinyl ketone  $\tilde{64}$  (198.1 ppm).



As in the enones, co-planarity of the components of the conjugated system in the dienones is the most important factor governing the position of the carbonyl chemical shift. Therefore, additivity parameters for substitution at the  $\alpha$ - and  $\beta$ -olefinic carbons must take into account changes from co-planarity due to steric effects. A greater extent of conjugation exists in the alicyclic dienones, the dienone ring being relatively planar in the molecules studied. The second double bond substitution effect in these dienones shields the carbonyl carbon to a greater extent (-13.3 ppm) than the introduction of the first double bond (-11.0 ppm) in the enones.

This study shows that the  $^{13}\text{C}$  spectrum provides diagnostic evidence for the identification and degree of co-planarity in the dienone cross-conjugated system. The statement of Marr and Stothers<sup>83</sup> (page 139) can be extended to cover dienones both acyclic and alicyclic with the dienone structure consisting of a contribution of the resonance forms which have conjugation between non-conjugated centers in the cross-conjugated system.

## E. EXPERIMENTAL

Some of the compounds studied are commercially available and were obtained from the following sources and were used without further purification. Aldrich Chemical Co., Inc., methyl vinyl ketone, mesityl oxide, butenone, phorone, p-benzoquinone, pulegone and cycloheptanone. Eastman Organic Chemicals, 1,5-diphenyl-3-pentadienone. A sample each of 4,4-dimethyl-2-cyclohexenone and isophorone was donated by Mr. E. Browne and Dr. P. Georghiou, respectively. The remaining compounds were prepared by well-known methods. The observed



physical constants and the synthesis employed are given below. In these cases the boiling points and melting points are uncorrected.

<u>Compound</u>	<u>Observed</u> <u>b.p./mm.</u>	<u>Reported</u> <u>b.p./mm.</u>	<u>Reference</u>
4,4-Dimethyl-2,5-cyclohexadienone	77-79/10	41/0.15	145
Piperitenone	120-125/10	125/10	146
2,6-Cycloheptadienone	65-66/2	50.5-51/1	147
2-Methyl-1,4-pentadien-3-one	62-65/100	59/95	148
2-Methyl-2,5-hexadien-4-one	60-65/20	60/22	148
2,4-Dimethyl-1,4-pentadien-3-one	75-78/100	72/110	89



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